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Drug Interactions

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Agenda

Drug interactions (DDI)
- Definition
- Significance

Pharmacokinetic DI - examples

Pharmacodynamic DI - examples

Pharmaceutical DI - examples

Drug interactions with food, beverages, herbs

Drug interactions among smokers

Recommendation

Summary

Definitions and Terms

Drug Interactions:“ The pharmacologic or clinical response to the administration of a drug combination different from that anticipated from the known effects of the two agents when given alone ”

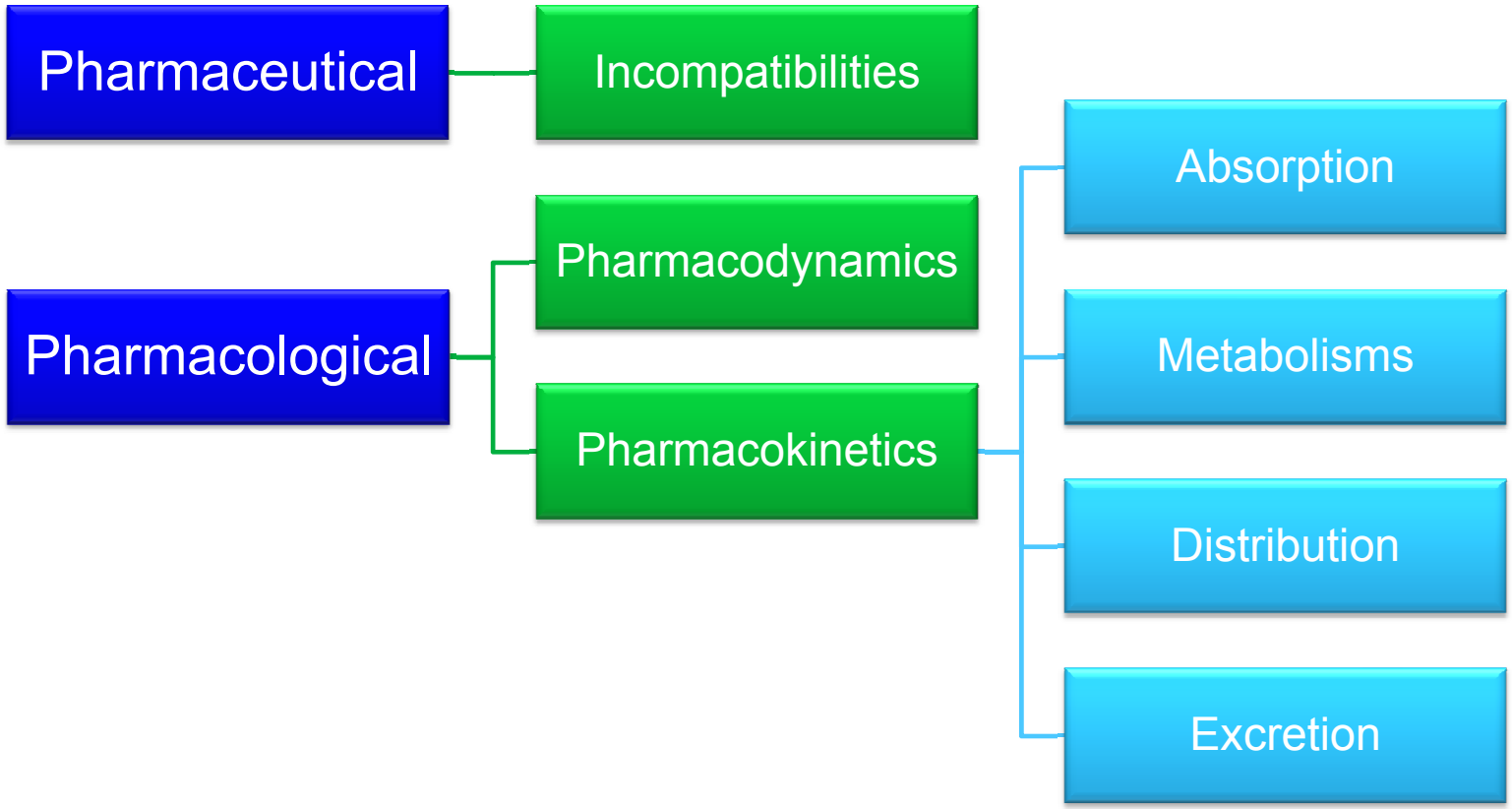
1Tatro DS (Ed.) Drug Interaction Facts. J.B. Lippincott Co. St. Louis 1992.

Negative?
Positive ?
Clinically relevant!

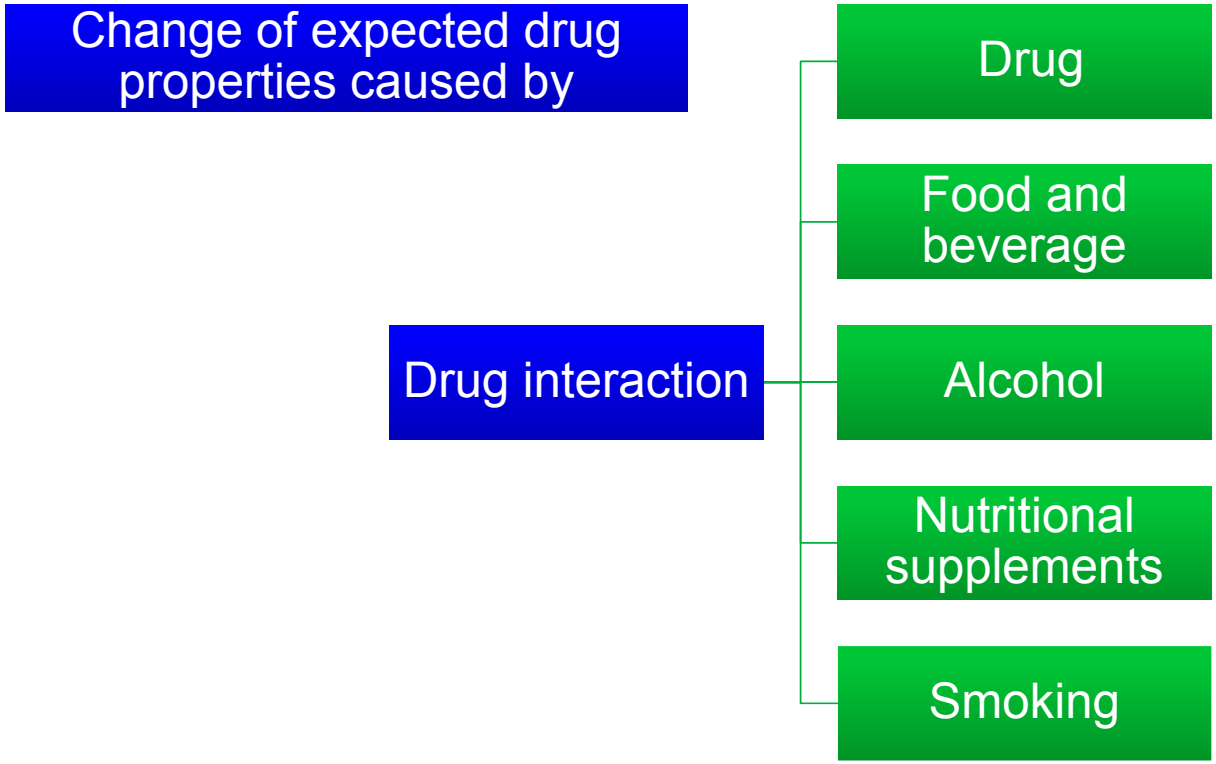
Classifying drug interactions

- Interrelationship 2 or more drugs at the level of:
  - **Pharmaceuticals** - physico-chemical and chemical interactions of the components
  - **Pharmacokinetics** – Involves absorption, distribution, metabolism and excretion, all of them being associated with both treatment failure or toxicity
  - **Pharmacodynamics** - interaction of active ingredients at the level
    - direct effect at receptor function,
    - interference with a biological or physiological control process and
    - additive/opposed pharmacological effect..

Drug interactions - classification



Drug interactions - classification



Classifying drug interactions

Grade	Relevance
1 – A	Nonrelevant
2 – B	Minor
3 – C	Moderate
4 – D	Major
5 – X	Contraindicated (?)

Significance of drug interactions

Desirable (beneficial for the patient)

- drug combination potentiating drug effect and decreasing the toxicity

combination of:

cytostatics
analgesics
antihypertensives
ATBs
drugs for asthma

Significance of drug interactions

Desirable (beneficial for the patient)

- combination of the active substance suppressing/inhibiting the effect of another drug
- in the treatment of intoxication/poisoning organism

toxic substance	Antidote
amanita phalloides	Silibin, N-acetylcystein
opiates	naloxon
atropine	fysostigmin
benzodiazepines	flumazenil
digitalis	antidigitalisová globulin
glycoles	ethanol, fomepizol
carbamates	atropine
kumarini	vitamin K
cyanides	amylium nitrosum, hydroxycobalamin,
aniline	methylene blue
lead	EDTA, DMSA
organophosphate	atropine, oximy
paracetamol	N-acetylcystein

Significance of drug interactions

Undesirable (for the patient harmful, potentially dangerous)

- Major - life threatening
- Moderate - clinically significant
- Minor

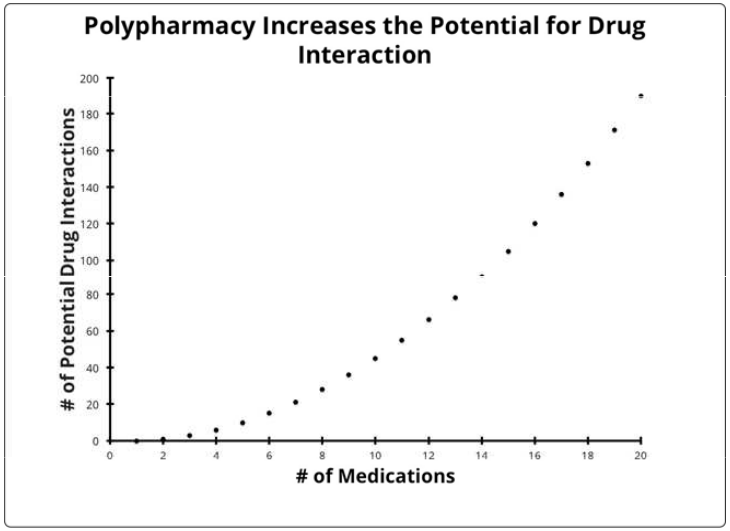
This may result in:

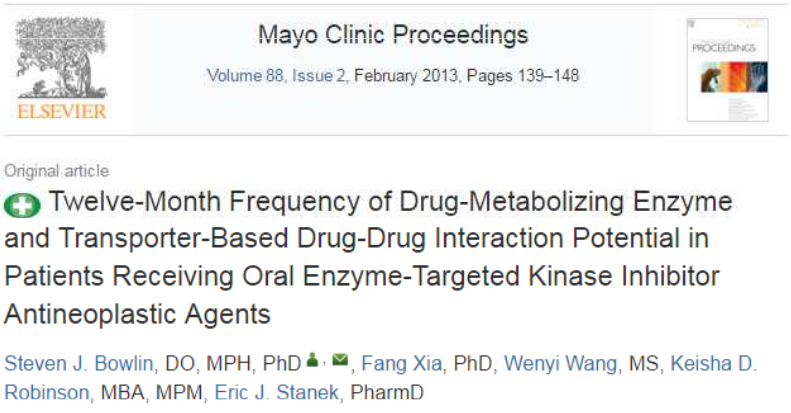
- increase or decrease (loss) effect
- increasing or reducing the incidence of side effects
- other changes in effect
- injury or even death

clinically insignificant

Why are the drug interactions so important?

- are one of the commonest causes of ADRs
- particularly in the elderly due to polypharmacy
- with a prevalence of 20-40% in population
- 75 % are preventable
- ADR are 4th most frequent cause of death





Leape LL et al. *JAMA* 1995;274(1):35–43.
Raschetti R et al. *Eur J Clin Pharmacol* 1999;54(12):959–963.

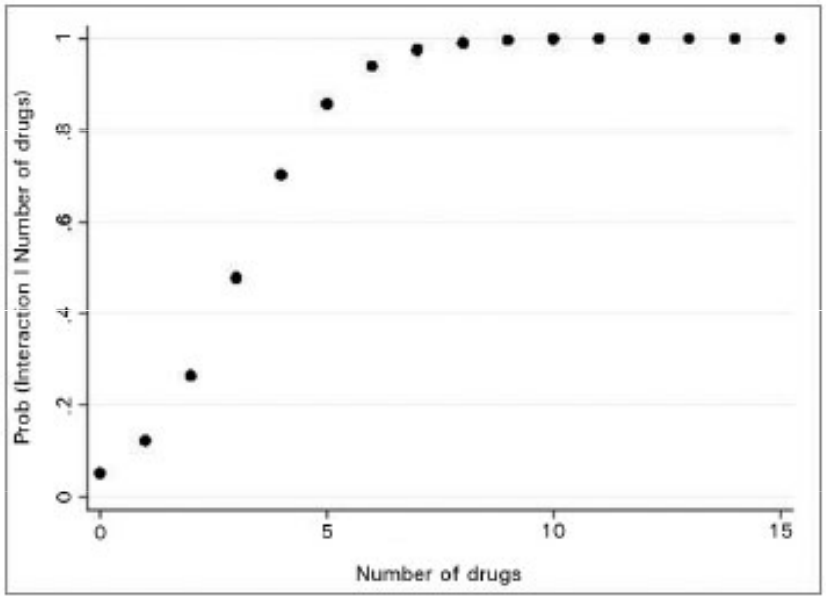
DDI risk factors

- Poly pharmacy
- Multiple prescribers
- Multiple pharmacies
- Genetic
- Specific population like elderly, obese, critically ill patient
- Specific illness e.g. Hepatic disease,
- Renal dysfunction…
- Narrow therapeutic index drugs

Digoxin, Warfarin, Insulin, Antidepressant, Lithium

The risk of polypharmacy

prescribing cascade **-** which occurs when an ADR is misunderstood and new potentially unnecessary drugs are administered; therefore the patient is at risk to develop further ADRs



May F.E., Stewart R.B., Cluff L.E.: Drug interactions and multiple drug administration. Clin.Pharmac.Ther. 1977, 22:322

ARTICLE

Potential Drug Interactions and Duplicate Prescriptions Among Cancer Patients

Rachel P. Riechelmann, Ian F. Tannock, Lisa Wang, Everardo D. Saad, Nathan A. Taback, Monika K. Krzyzanowska

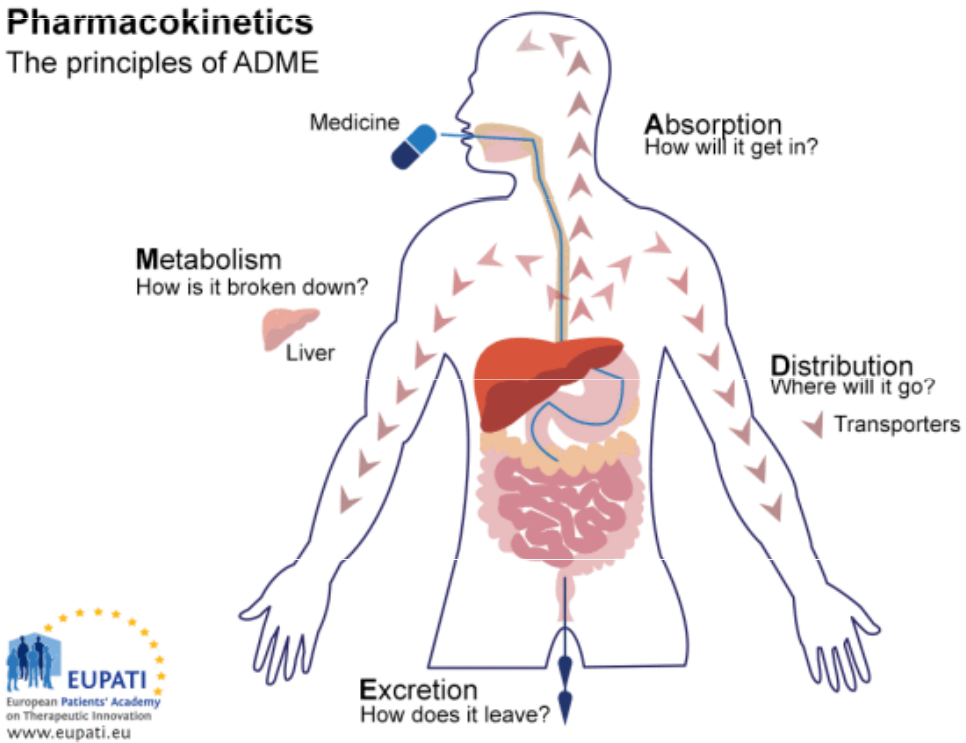
J Natl Cancer Inst 2007;99:592–600

Consequences of drug interactions

1. Loss of therapeutic effect
2. Toxicity
3. Unexpected increase in pharmacological activity
4. Beneficial effects e.g additive & potentiation (intended) or antagonism (unintended).
5. Chemical or physical interaction e.g I.V incompatibility in fluid or syringes mixture

Pharmacokinetics drug interactions

Pharmacokinetics drug interactions



Pharmacokinetics drug interactions

- are often considered on the basis of knowledge of each drug and are identified by controlling the **patient's clinical manifestations** as well as the changes in **serum drug concentrations**.

They involved all the processes from absorption up to excretion.

Pharmacokinetic interactions
- Absorption

- altered pH
- altered bacterial flora
- formation of drug chelates or complexes
- drug induced mucosal damage
- altered GIT motility

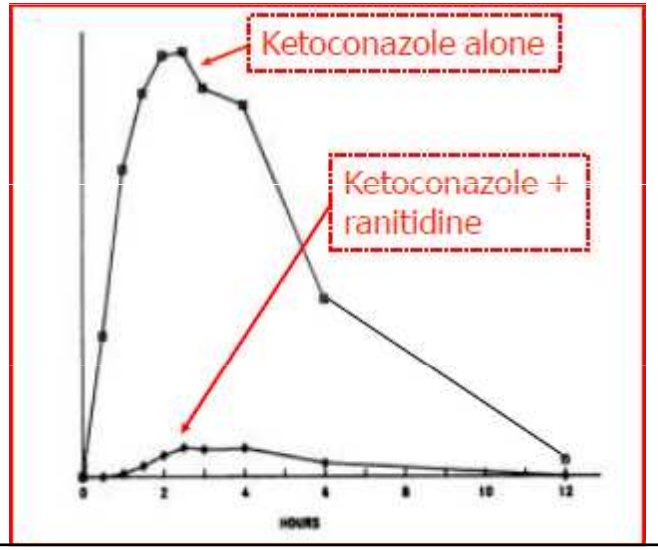
Altered pH

The non-ionized form of a drug is more lipid soluble and more readily absorbed from GIT than the ionized form does.

Antacids →
PPI →
H2 antagonists →

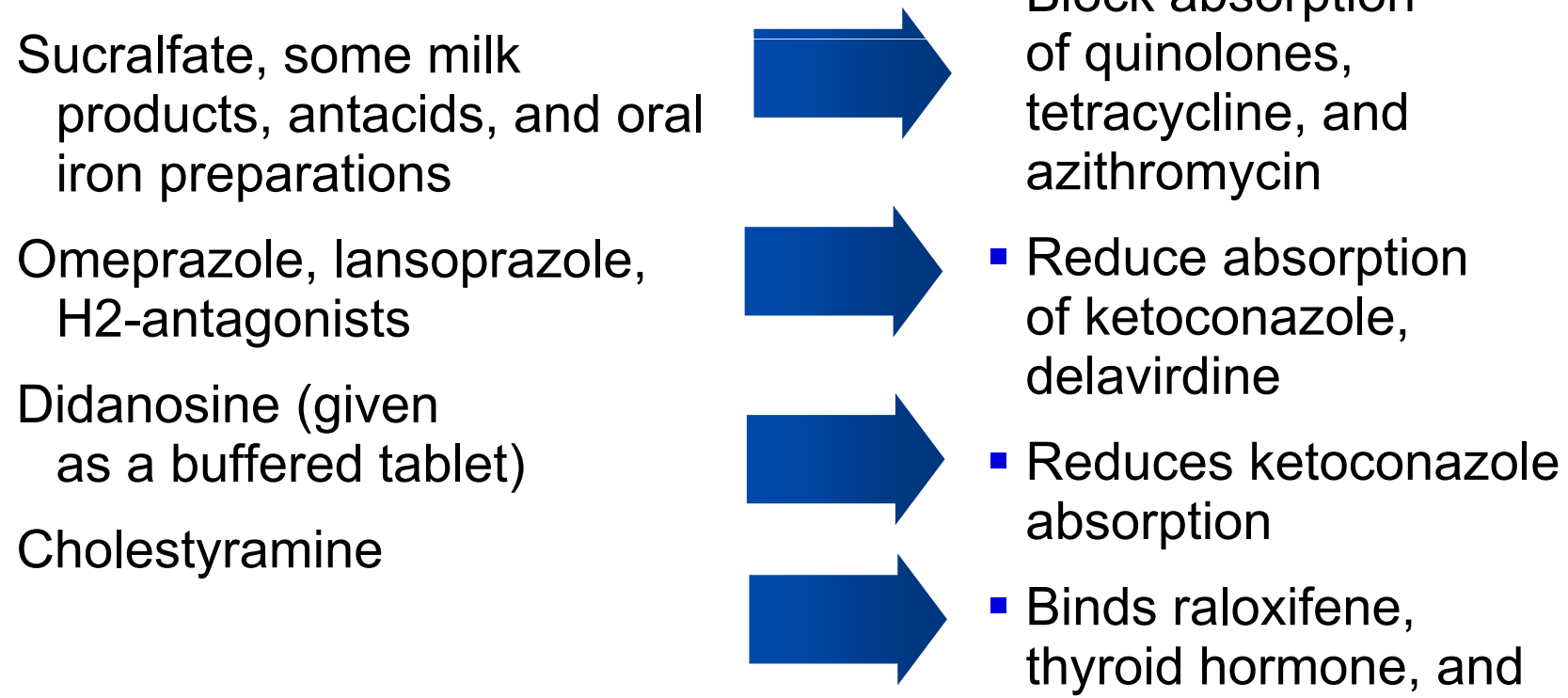
Decrease the tablet dissolution of Ketoconazole (acidic)

Therefore, these drugs must be separated by at least 2h in the time of administration of both.



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC245265/?page=2

They Can Occur in the GI Tract



Tyrosinkinase inhibitors/azole antimycotics And drugs lowering gastric pH

TKI/azole antimycotics

- sunitinib
- Gefitinib
- Sorafenib
- Bosutinib
- imatinib

- Voriconazole
- Fluconazole

Drugs lowering gastric pH

- omeprazol
- pantoprazol
- famotidin
- ranitidin

- Antacids

Decreased absorption and availability of TKI/azole antimycotics

Altered intestinal bacterial flora

- 40% or more of the administered digoxin dose is metabolised by the intestinal flora.
- Antibiotics kill a large number of the normal flora of the intestine

Increase digoxin conc. and increase its toxicity

Complexation or chelation

Tetracyclines, Quinolones interact with iron, calcium, magnesium, aluminium preparations

or

Milk (Ca^{2+}) → **Unabsorpable complex**

Antacid (aluminum or magnesium) hydroxide

Decrease absorption of ciprofloxacin by 85% due to chelation

carbo medicinalis (coal), diosmectin – readsorption of other drugs

Drug-induced mucosal damage

Antineoplastic agents

cyclophosphamide, vincristine, procarbazine

Inhibit absorption
of several drugs
eg., digoxin

Altered motility

Increased motility

- Diarrhea - reduce absorption
- Prokinetic drugs - metoclopramide, domperidone, itopride

Decreased motility

- Ileus, constipation - increase in AUC of drugs, toxicity
- Opioids, diphenoxylate, loperamide

Pharmacokinetic interactions - Distribution

- The major plasma proteins to which most drugs bind are **albumin** and **a1-acid glycoprotein**; the former typically binds acidic, anionic drugs whereas the latter typically favors basic drugs
- Competitive protein binding by another drug will result in increase concentration of free drug, and that will yield more drug response

Maximum Fraction Bound in Plasma ($ß_{max}$)	Fraction of Total Drug Bound in the Body	Maximum Possible Increase in Pharmacodynamic Effect Due to Complete Binding Displacement
50%	10%	10%
90%	49.6%	~ two-fold
99%	91.5%	~ 12-fold

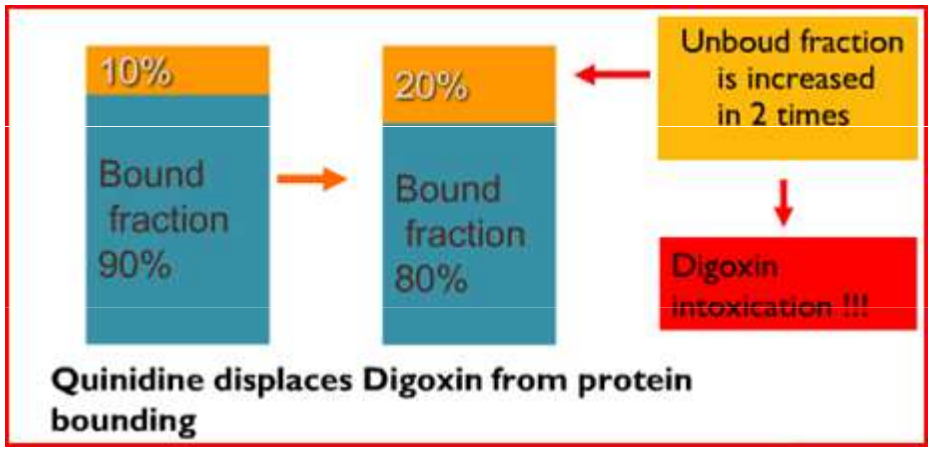
Displaced protein binding

- **It depends on the affinity of the drug to plasma protein. The most likely bound drugs is capable to displace others.**
- It is clinically important if displaced drug is highly PP binding , with LONG T ½, small Vd, narrow therapeutic range.
- **The free drug is increased by displacement by another drug with higher affinity.**

Aspirin, Phenylbutazone, Clofibrate

Displace:

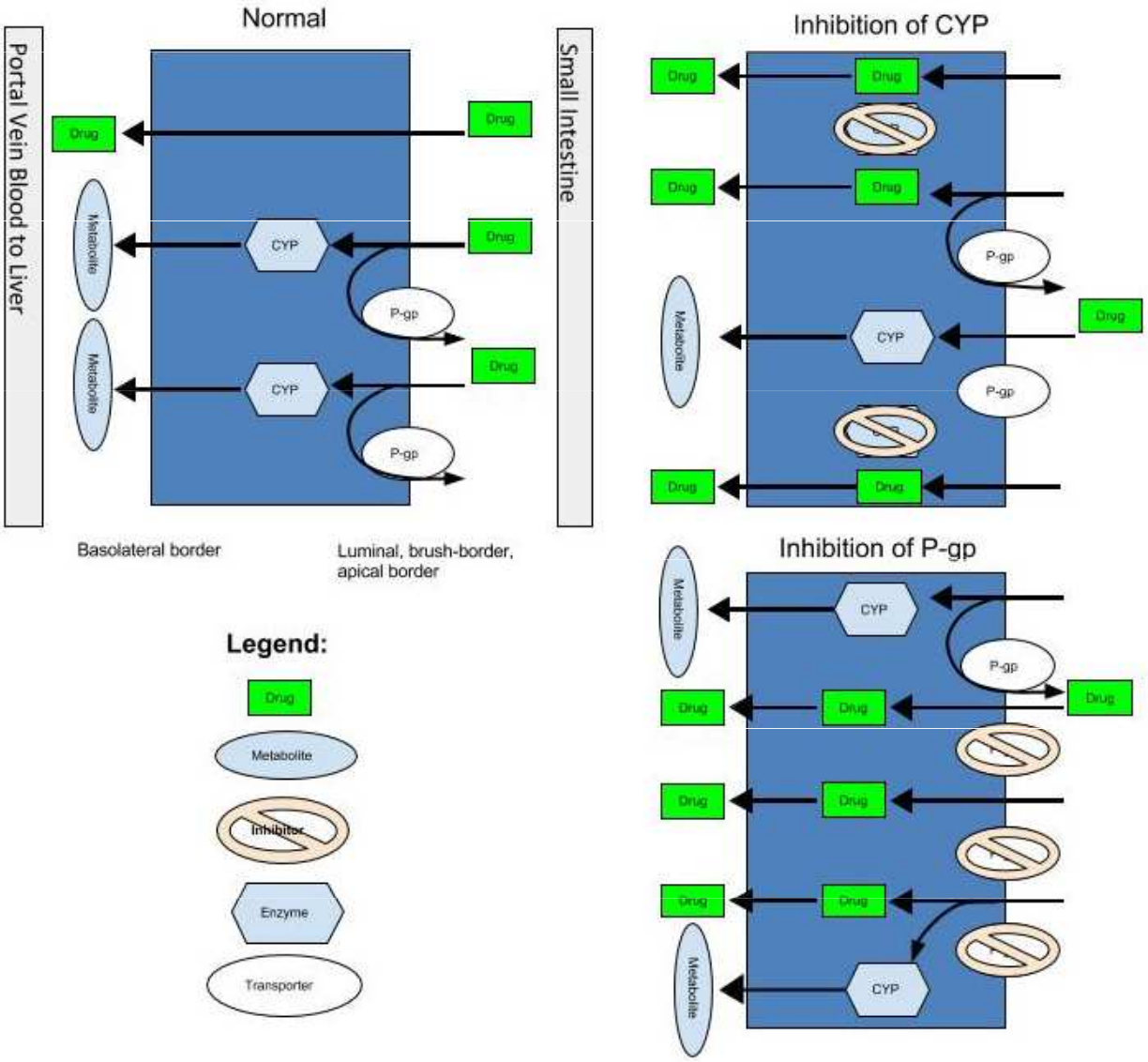
- Oral Anti-coagulants (Dicumarol, Warfarin)
  - Bleeding
- Oral Hypoglycemics (Tolbutamide)
  - Hypoglycemia
- Bilirubin in Neonate
  - Jaundice & Kernictrus.
- Phenytoin



Drugs binding to protein

Drugs EXTENSIVELY bound (>90%)	**Drugs *BARELY* bound (<10%)**
Oral anticoagulants: warfarin ***Oral antidiab.:*** glimepiride, glipizide, glyburide ***Lipid lower. drugs:*** gemfibrozil, statins ***NSAID:*** indomethacine, phenylbutazone ibuprofen, naproxen, diflunisal, diclophenac ***Loop diuretics,*** e.g. furosemide ***Antihypertensives:*** diazoxide, losartan ***Cardiovasc:*** amiodarone, prazosin, felodipine, nicardipine, digitoxin, ticlopidine ***Antiinfectives:*** ceftriaxone, nalidixic acid, ketoconazole, itraconazole, suramin, nelfinavir ***Benzodiazepines:*** diazepam, midazolam ***Others:*** montelukast, zafirlukast, entacapone leflunomide	**aminoglycosides**, e.g. gentamycin **flucytosine, fluconazole** **isoniazid** **ifosfamide** **metformin** **codeine** **metoprolol, tocainide** **ouabain (strophantin)** **lisinopril** **lithium** **ethanol**
Drugs with INTERMEDIATE binding – examples: **phenytoin (89%), carbamazepine (74%), phenobarbital (60%), theophylline (60%), hydrochlorothiazide (58%), aspirin (50%), paracetamol = acetaminophen (20%)**	

Illustration 1: Intestinal Enterocytes



Selected P-Glycoprotein Substrates[20,22–24,59]

Anticancer agents
- Doxorubicin
- Docetaxel[a]
- Vincristine[a]
- Vinblastine[a]
- Etoposide[a]
- Actinomycin D

Steroid hormones
- Aldosterone
- Cortisol[a]
- Dexamethasone[a]
- Methylprednisolone

Antimicrobial agents
- Erythromycin[a]
- Ketoconazole
- Itraconazole[a]
- Tetracycline
- Doxycycline
- Levofloxacin
- Sparfloxacin

Opioids
- Loperamide
- Morphine
- Butorphanol

Cardiac drugs
- Digoxin
- Diltiazem[a]
- Verapamil[a]
- Talinolol

Immunosuppressants
- Cyclosporine[a]
- Tacrolimus[a]

Miscellaneous
- Ivermectin and other avermectins
- Amitriptyline
- Terfenadine[a]
- Ondansetron
- Domperidon
- Acepromazine
- Vecuronium

[a]Substrate of CYP3A.

Selected P-Glycoprotein Inhibitors[19,22,25,35,60,61]

Antidepressants
- Fluoxetine
- Saint John's Wort
- Paroxetine

Antimicrobials
- Erythromycin[a,b]
- Itraconazole[a]
- Ketoconazole[a,b]

Opioids
- Methadone
- Pentazocine

Cardiac drugs
- Verapamil[a]
- Amiodarone[a]
- Carvedilol
- Quinidine[a]
- Nicardipine[a]

Immunosuppressants
- Cyclosporine[a]
- Tacrolimus[a]

Miscellaneous
- Bromocriptine
- Chlorpromazine
- Tamoxifen[a]
- Grapefruit juice[b]

[a]CYP3A substrate.
[b]CYP3A inhibitor.

http://www.vetfolio.com/pharmacology/adverse-drug-reactions-in-herding-breed-dogs-the-role-of-p-glycoprotein

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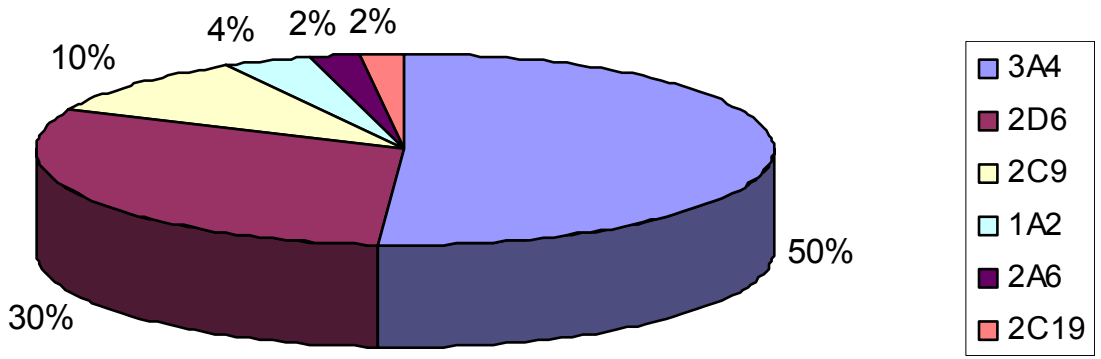
Pharmacokinetic interactions - Metabolism

The effect of one drug on the metabolism of the other is well documented. The liver is the major site of drug metabolism but other organs can also do e.g., WBC, skin, lung, and GIT.
CYP450 family is the major metabolizing enzyme in phase I (oxidation process). Therefore, the effect of drugs on the rate of metabolism of others can involve the following examples



Polymorphism of enzymes

- slow metabolizer - all defective alleles
- medium metabolizer - an intact allele
- rapid metabolizer - all intact allele (wild type)
- ultrarapid metabolizer - multiplication of a gene or a higher enzyme activity

CYP P450

a key enzyme in the metabolism of xenobiotics
mainly responsible for Phase I biotransformation processes
occurring in the liver, lungs, kidneys, brain, skin, small intestine and other organs

- Substrates P450
  - drug metabolizing by this enzyme
- Inhibitors of cytochrome P450
  - accumulation of the drug in the body
  - increased plasma levels
  - Increased toxicity
- Inducers of Cytochrome P450
  - increased degradation of the drug from the organism
  - subtherapeutic plasma levels of the drug
  - reduce the effect of drugs

Substrates

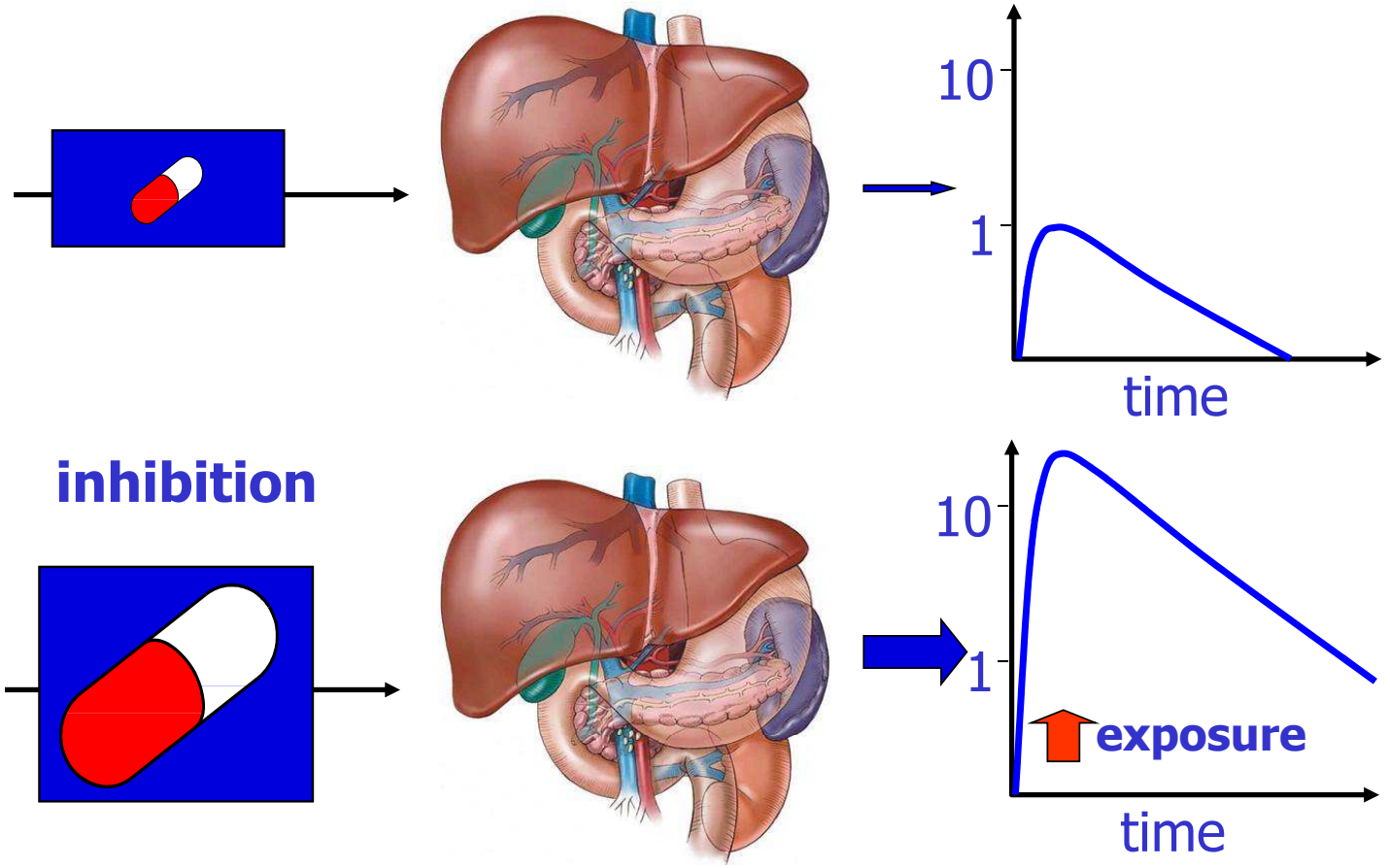
high interindividual variability

high interindividual variability

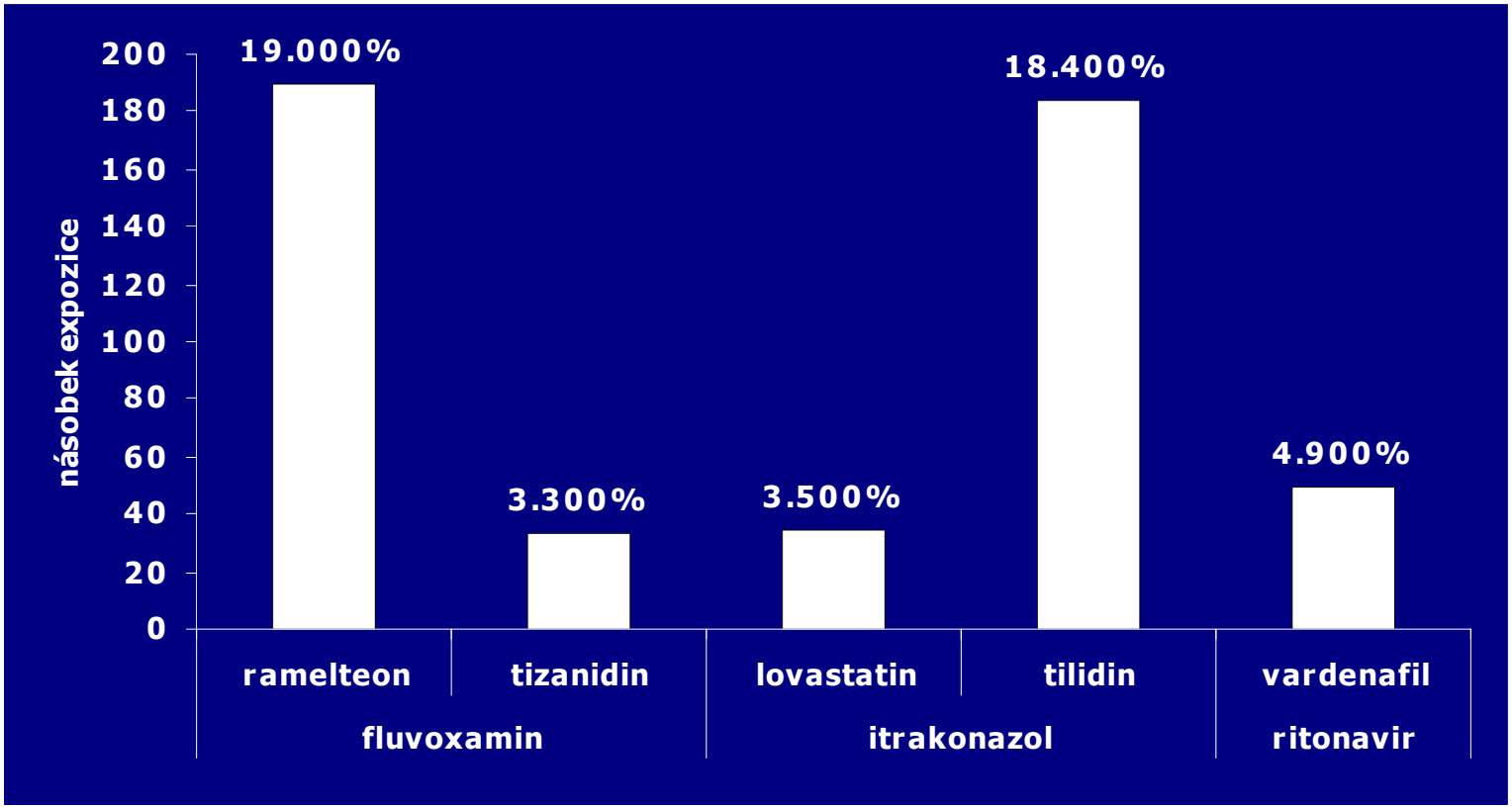
high interindividual variability

Izoformy cytochromu P450					
CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP2E1	CYP3A4
Kofein	Amitriptylin	Amitriptylin	Amitriptylin	Acetaminofen	Alprazolam
Klozapin	Citalopram	Celecoxib	Clomipramin		Astemizol
Fuvoxamin	Clomipramin	Diklofenak	Kodein	Dapson	Buspiron
Imipramin	Cyklofosfamid	Ibuprofen	Dextrometorfan	Ethanol	Blokátory Ca^{2+} kanálů
Mexiletin	Diazepam	Losartan	Imipramin	Isofluran	Karbamazepin
Olanzapin	Imipramin	Naproxen	Metoprolol	Isoniazid	Cyklosporin
Propranolol	Lanzoprazol	Fenytoin	Oxykodon		Doxorubicin
Teofylin	Omeprazol	Sulfamethoxazol	Paroxetin		Etoposid
Warfarin	Fenytoin	Warfarin	Propafenon		Fentanyl
			Tramadol		Midazolam
			Venlafaxin		Simvastatin
					Takrolimus

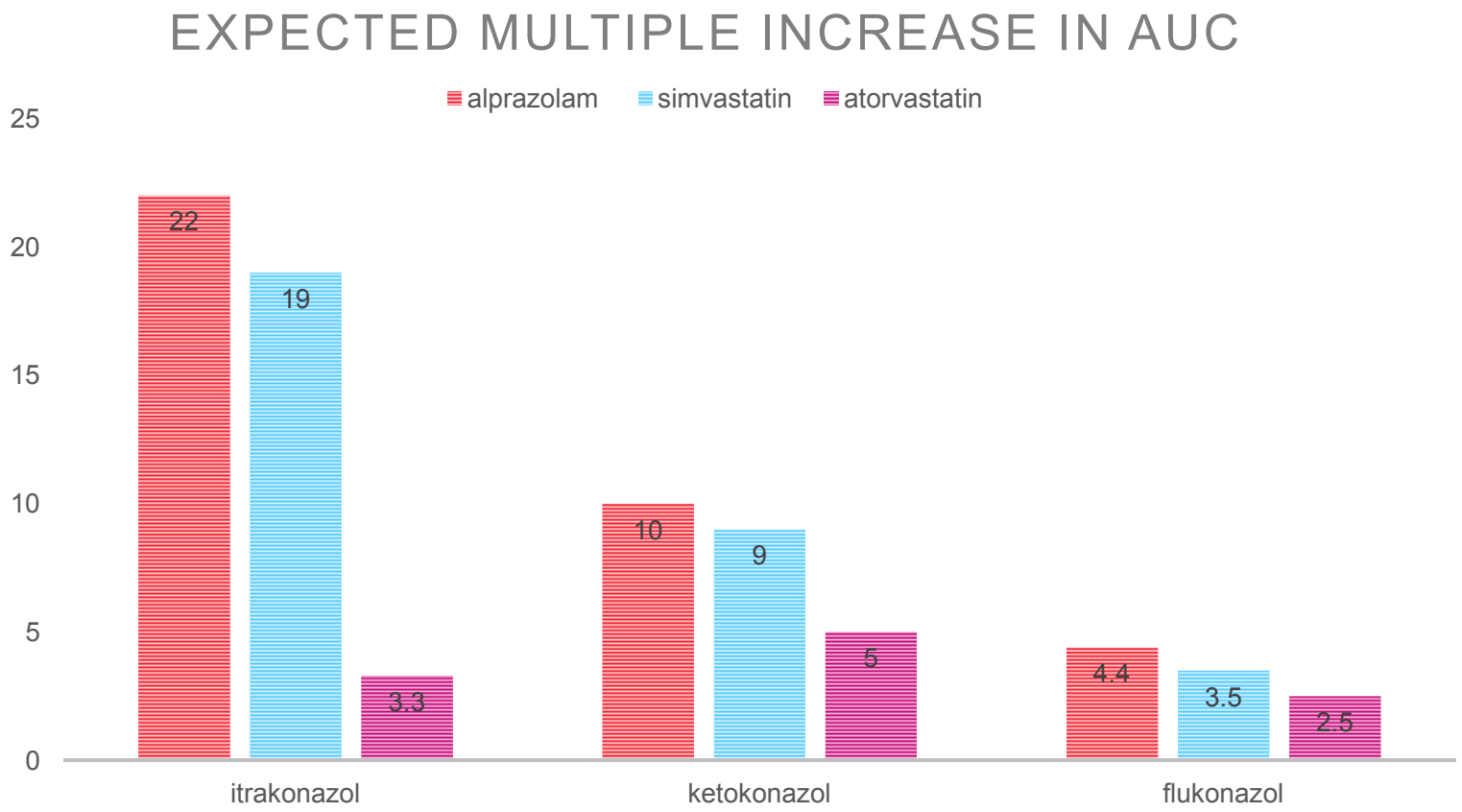
Basic mechanisms - inhibition



Significant drug interactions - inhibition



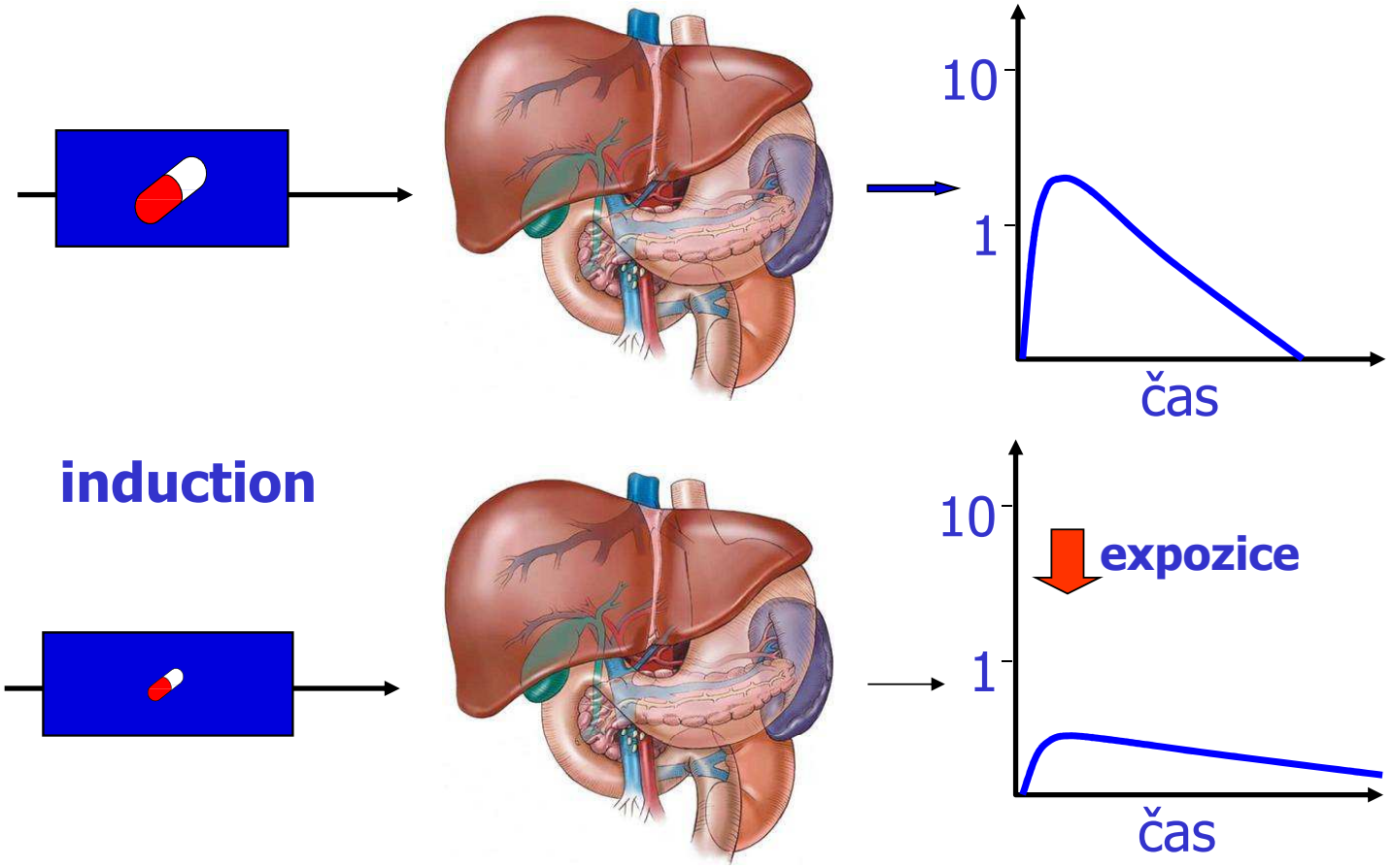
Different inhibiting ability of drugs from the same ATC



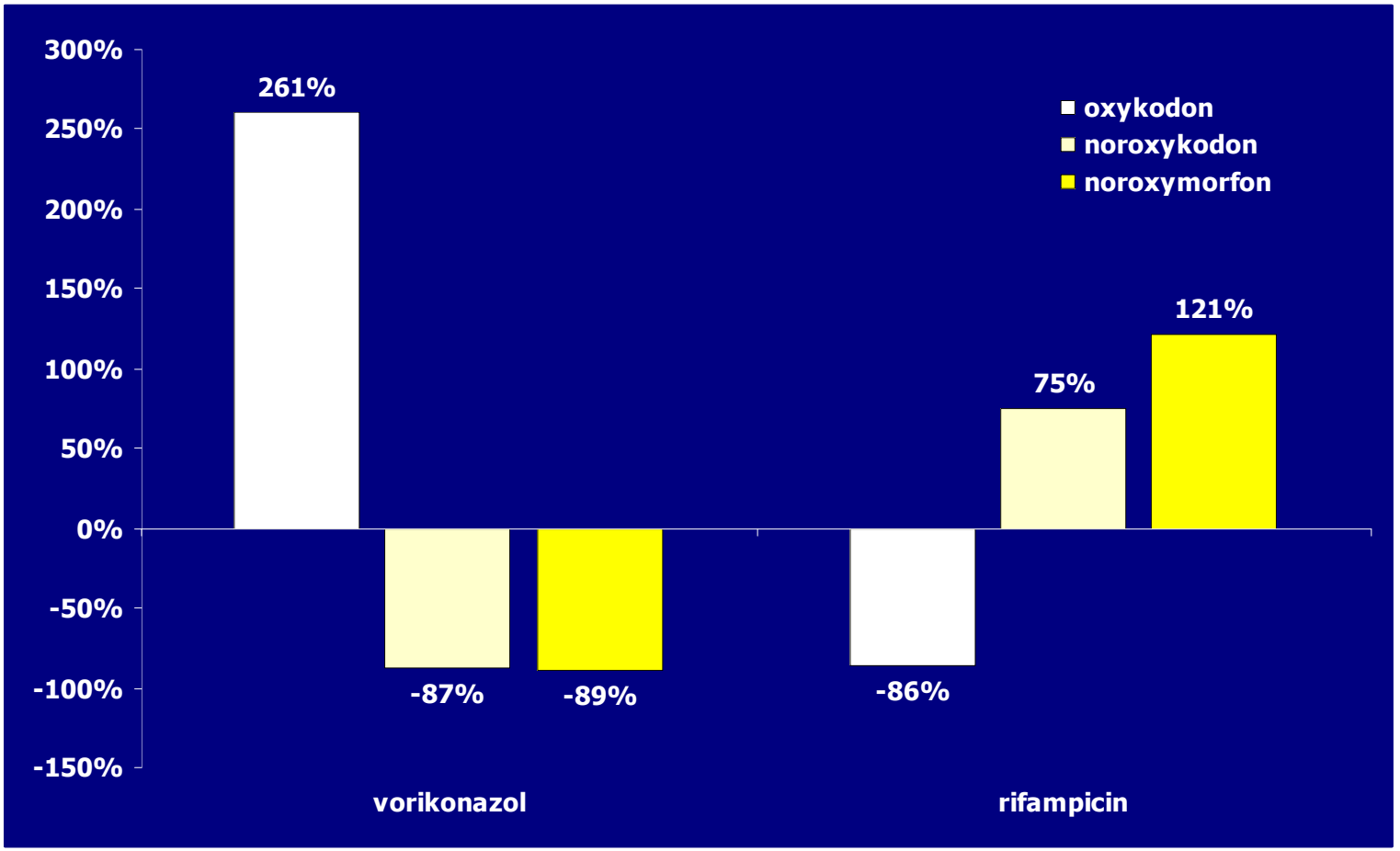
Inhibitors

CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP2E1	CYP3A4
Cimetidin	Cimetidin	Amiodaron	Amiodaron	Disulfiram	Amiodaron
Ciprofloxacin	Fluoxetin	Flukonazol	Fluoxetin		Cimetidin
Citalopram	Fluvoxamin	Fluoxetin	Haloperidol		Cyklosporin
Diltiazem	Ketokonazol	Fluvastatin	Indinavir		Diltiazem
Enoxacin	Lanzoprazol	Isoniazid	Paroxetin		Flukonazol
Fluvoxamin	Omeprazol	Metronidazol	Propafenon		Grepová šťáva
Ofloxacin	Paroxetin	Paroxetin	Ritonavir		Inhibitory HIV proteázy
Tiklopidin	Tiklopidin	Fenylbutazon	Sertralin		Itrakonazol
		Sulfamethoxazol / trimethoprim	Tiklopidin		Ketokonazol
		Tiklopidin			Makrolidová antibiotika (vyjma azithromycinu)
					Omeprazol
					Ritonavir
					Verapamil

Basic mechanisms - induction

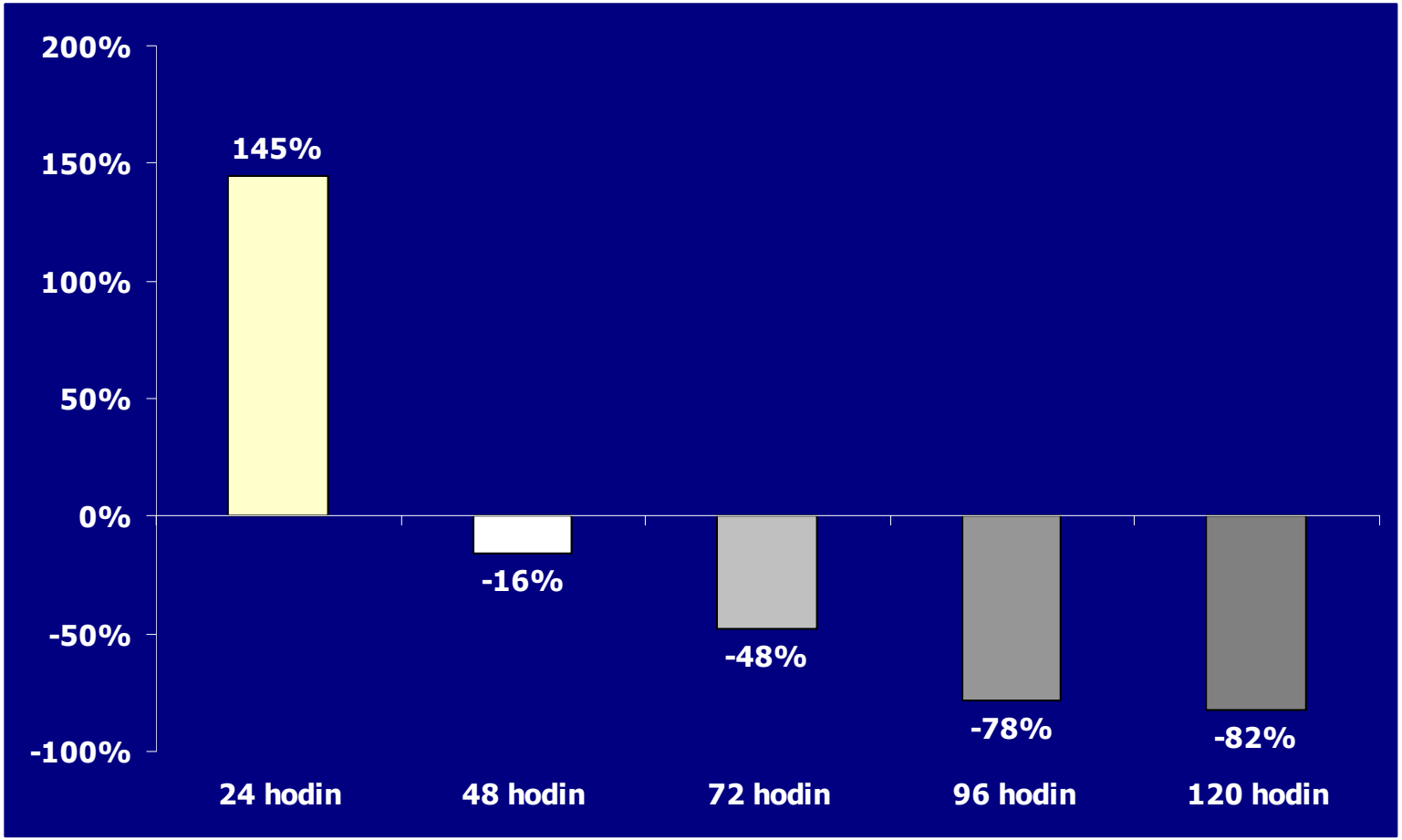


Drug interactions - induction



AUC (%)

Drug interactions – slow onset of induction



AUC (%)

Inductors

CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP2E1	CYP3A4
Karbamazepin	Karbamazepin	Fenobarbital		Chronicky užívaný alkohol	Dexamethason
Tabákový kouř	Třezalka tečkovaná	Rifampicin		Isoniazid	Fenobarbital
		Třezalka tečkovaná		Tabákový kouř	Fenytoin
					Karbamazepin
					Rifabutin
					Rifampicin
					Ritonavir
					Troglitazon
					Třezalka tečkovaná

It may be seconds up to weeks for example in case of enzyme induction, it needs weeks for protein synthesis, while enzyme inhibition occurs rapidly.

Pharmacodynamics drug interactions

Pharmacodynamics drug interactions

It means alteration of the dug action without change in its serum concentration by pharmacokinetic factors.

Additive effect : $1 + 1 = 2$

Synergistic effect : $1 + 1 > 2$

Potentiation effect : $1 + 0 = 2$

Antagonism : $1 - 1 = 0$

Pharmacodynamics drug interactions - examples

Drugs	Result of interaction
Anticholinergics + anticholinergics (anti-parkinsonian agents, butyrophenones, phenothiazines, tricyclic antidepressants, etc.)	Increased anticholinergic effects; heat stroke in hot and humid conditions; adynamic ileus; toxic psychoses
Antihypertensives + drugs causing hypotension (anti-anginals, vasodilators, phenothiazines)	Increased antihypertensive effects; orthostasis
CNS depressants + CNS depressants (alcohol, anti-emetics, antihistamines, hypnosedatives, etc.)	Impaired psychomotor skills, reduced alertness, drowsiness, stupor, respiratory depression, coma, death
QT prolonging drugs + other QT prolonging drugs (Amiodarone + Disopyramide)	Additive prolongation of QT interval, increased risk of torsade de pointes
Methotrexate + co-trimoxazole	Bone marrow megaloblastosis due to folic acid antagonism
Nephrotoxic drugs + nephrotoxic drugs (genta-micin or tobramycin with cefalotin (cephalothin)	increased nephrotoxicity
Neuromuscular blockers + drugs with neuromuscular blocking effects (e.g. aminoglycoside antibacterials)	Increased neuromuscular blockade; delayed recovery, prolonged apnoea
Potassium supplements + potassium-sparing diuretics (triamterene)	Marked hyperkalaemia

QT interval prolongation

TKI

Sorafenib
Sunitinib
Pazopanib
Dasatinib
Nilotinib

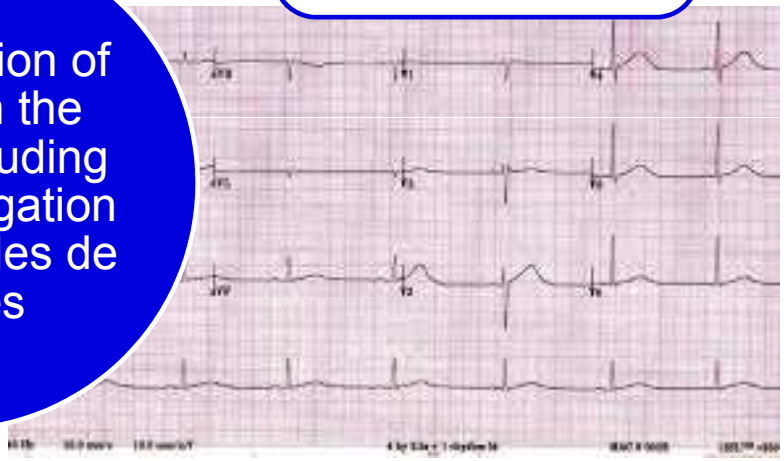
+

CYP 3A4
Inhibitors
claritromycin
ciprofloxacin

+

amiodaron
sotalol
ondansetron
propafenon
chlorpromazine
haloperidol
cisapride
domperidon
pimozide

Deterioration of ADRs on the heart, including QT prolongation and torsades de pointes



Opposing or antagonistic interactions

Drug affected	Interacting drugs	Results of interaction
Anticoagulants	Vitamin K	Anticoagulant effects opposed
Carbenoxolone	Spironolactone	Ulcer-healing effects opposed
Hypoglycaemic agents	Glucocorticoids	Hypoglycaemic effects opposed
Hypnotic drugs	Caffeine	Hypnosis opposed
Levodopa	Antipsychotics (those with Parkinsonian side effects)	Antiparkinsonian effects opposed

Important Drug Interactions in the Elderly

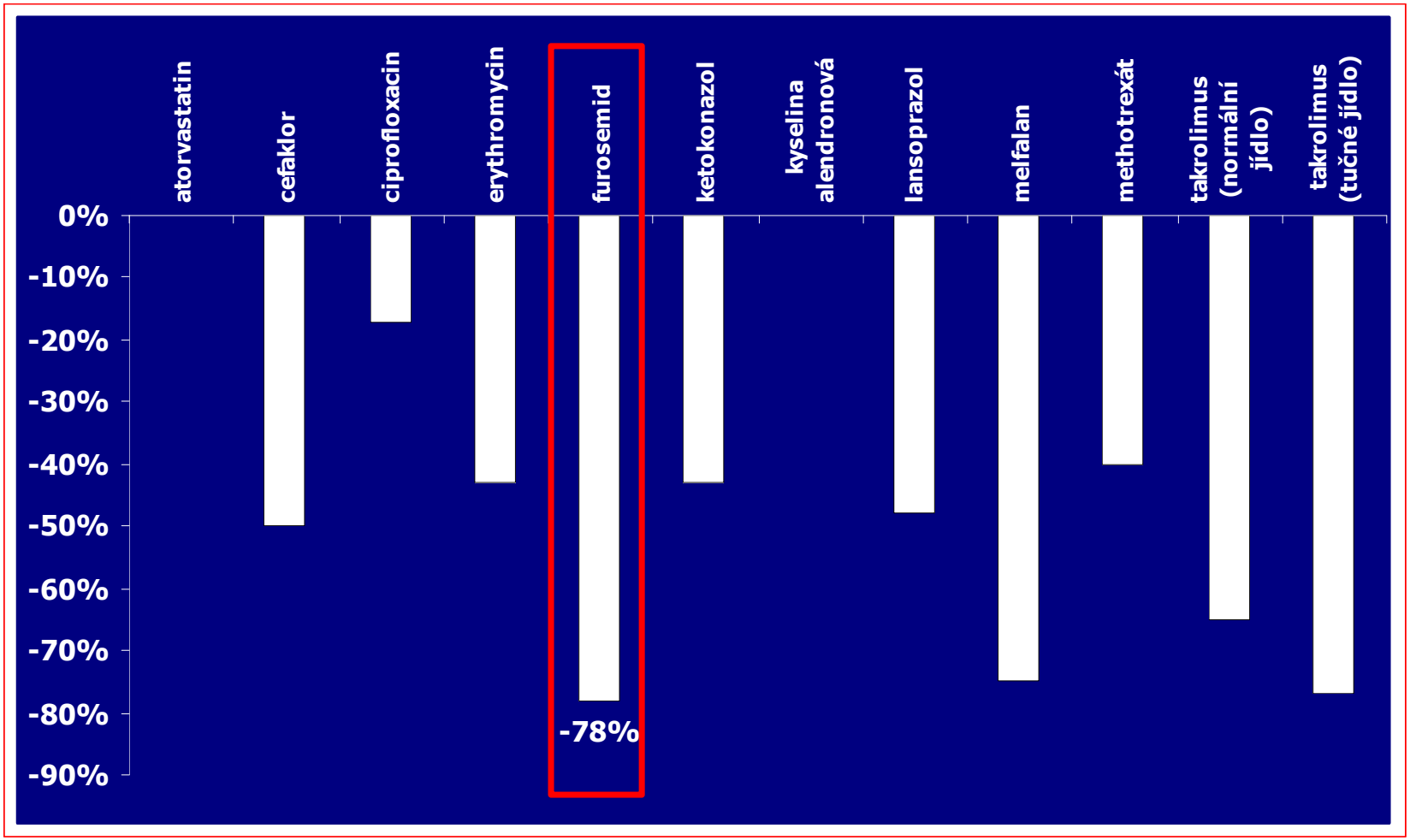
Drug–Drug Interaction	Observed Adverse Outcome
ACE inhibitors + K-sparing diuretics	Hospitalization for hyperkalemia
ACE inhibitors + co-trimoxazole	Hospitalization for hyperkalemia
Benzodiazepines + CYP3A4 inhibitors	Hospitalization for hip fracture
Calcium channel blockers + macrolides	Hospitalization for hypotension or shock
Digoxin + macrolides	Hospitalization for digoxin toxicity
Lithium + ACE inhibitors, loop diuretics	Hospitalization for lithium toxicity
Phenytoin + co-trimoxazole	Hospitalization for phenytoin toxicity
Glipizide or glyburide + CYP2C9 inhibitors	Hospitalization for hypoglycemia
Tamoxifen + paroxetine	Death from breast cancer
Theophylline + ciprofloxacin	Hospitalization for theophylline toxicity
Warfarin + co-trimoxazole or fluconazole	Hospitalization for GI bleeding
Warfarin + NSAIDs	Hospitalization for GI bleeding

.

ACE = angiotensin-converting enzyme; CYP = cytochrome P450; GI = gastrointestinal; K = potassium; NSAIDs =nonsteroidal anti-inflammatory drugs

Drug interactions with food, drinks, herbs

Drugs in which food reduces bioavailability



AUC (%)

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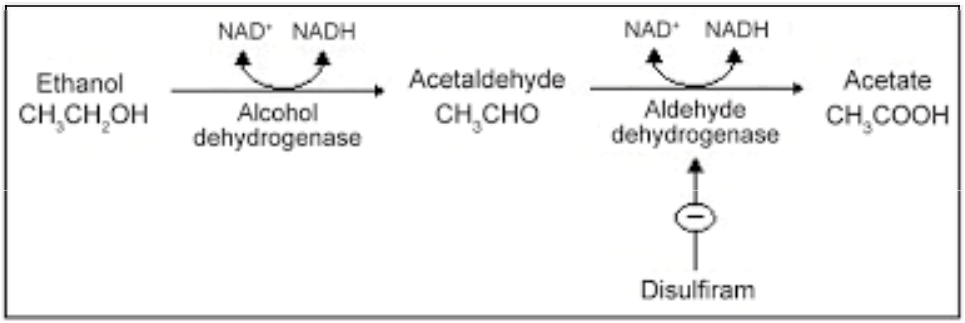
Furosemide before or after a meal?

- Furon® does not mentioned in SPC
- Furorese® fasting
- Slovakofarma® furosemide after meal

- Food in healthy volunteers (n = 18) resulted in a 45% reduction in the furosemide (40 mg) curve, a 78% reduction in peak plasma concentrations and a reduction in absolute bioavailability from 76% to 43% and a decrease in diuretic effect.
- Furosemide should be administered one hour before or 2 hours after a meal.

Inhibition of alcohol metabolism

- Disulfiram reaction:
- facial flushing associated with nausea, palpitations and hot flashes, collapse, arrhythmia, syncope, unconsciousness, convulsions



- disulfiram
- griseofulvin
- metronidazole
- co-trimoxazole (Biseptol®)
- cephalosporins (eg cefamandole, cefmenoxime, cefoperazone, cefotetan)
- ketoconazole
- tolbutamide
- furazolidone
- levamisol

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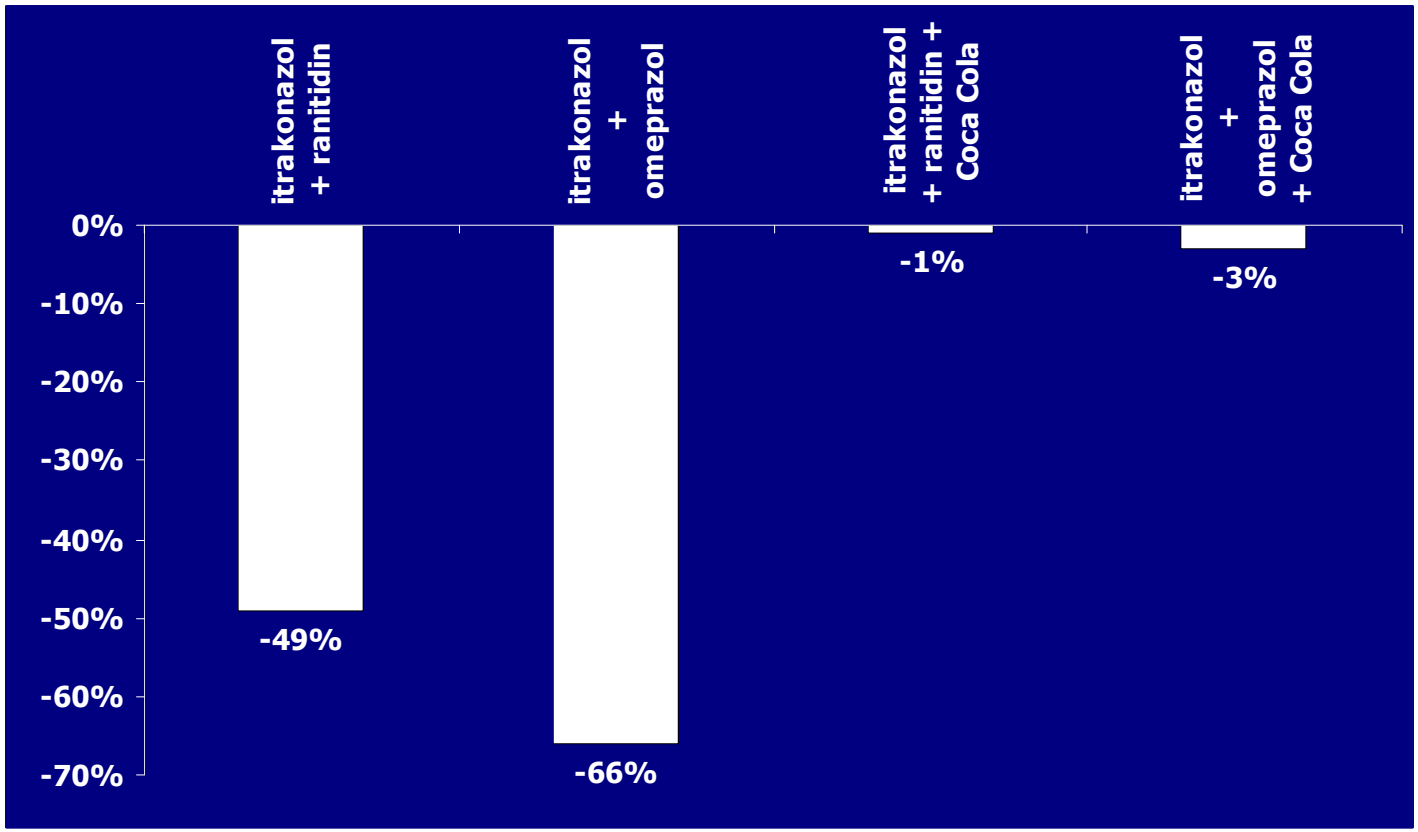
Coca-Cola® phenomenon



ACU (%)

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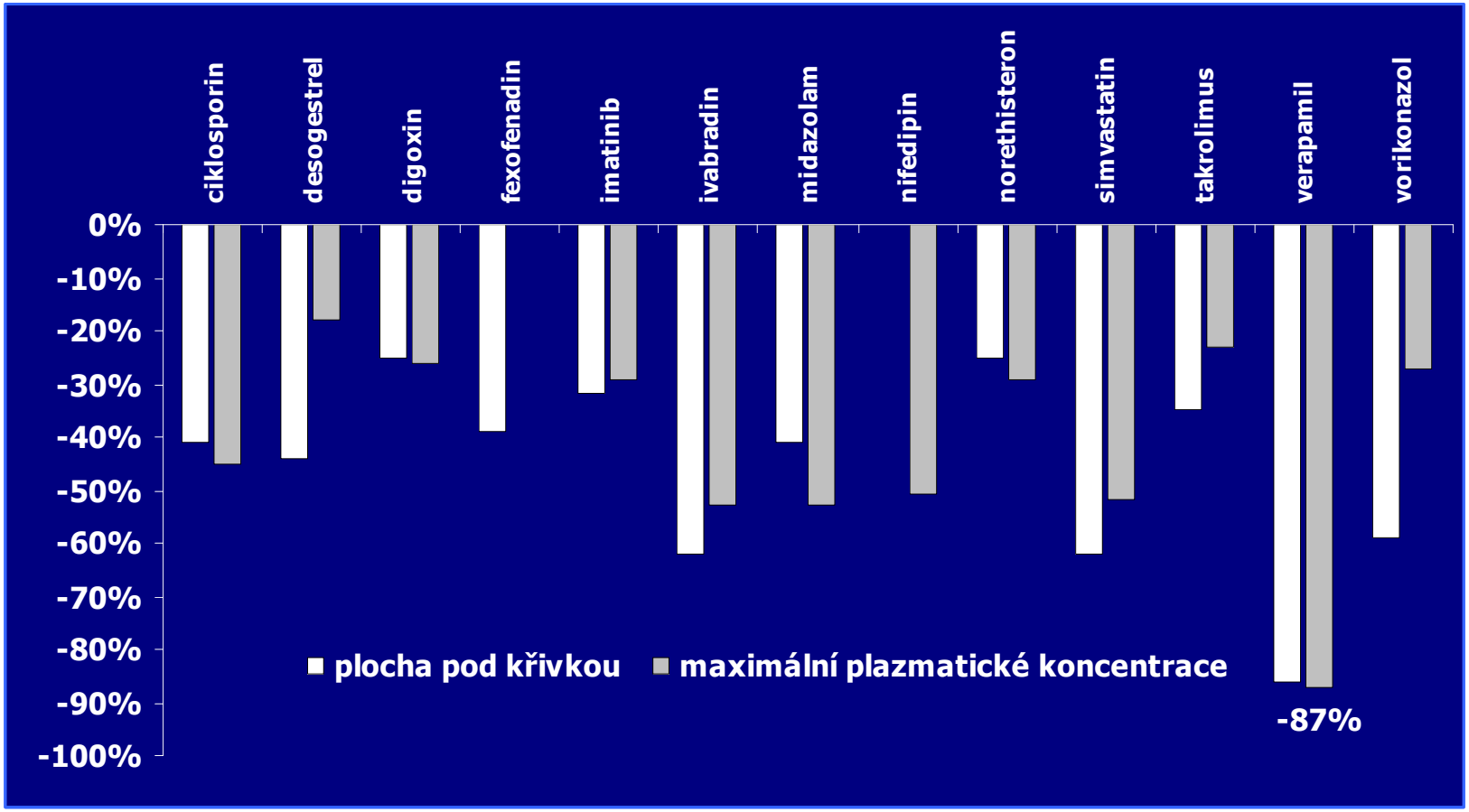
Foods as CYP modulators

- St John's wort
- CYP3A4 inducer
- CYP2C19 inducer
- CYP2C9 inducer
- P-glycoprotein inducer
- affecting (reducing to loss) the effect of many drugs that are substrates of CYP3A4 or P-glycoprotein

St John's wort



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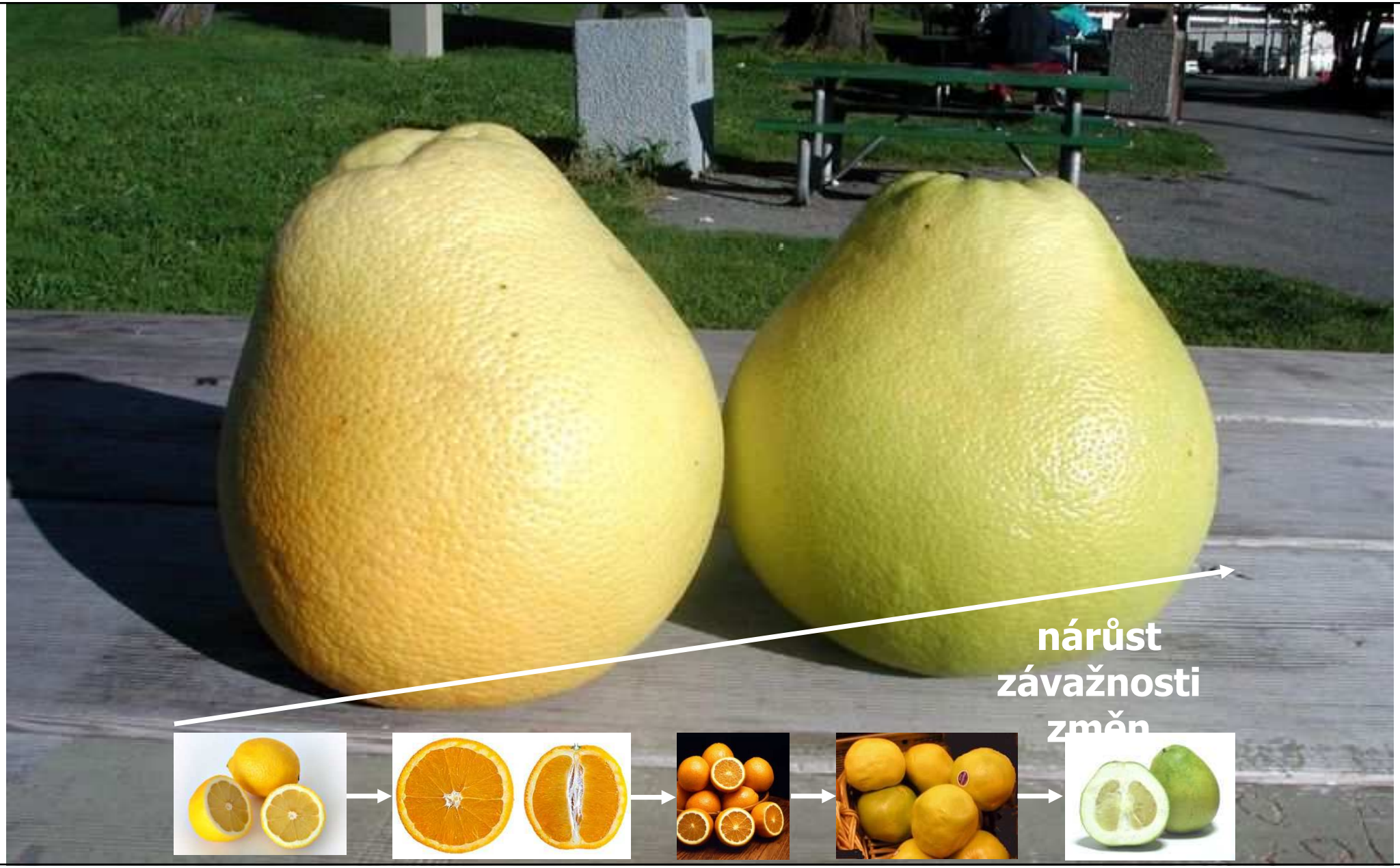
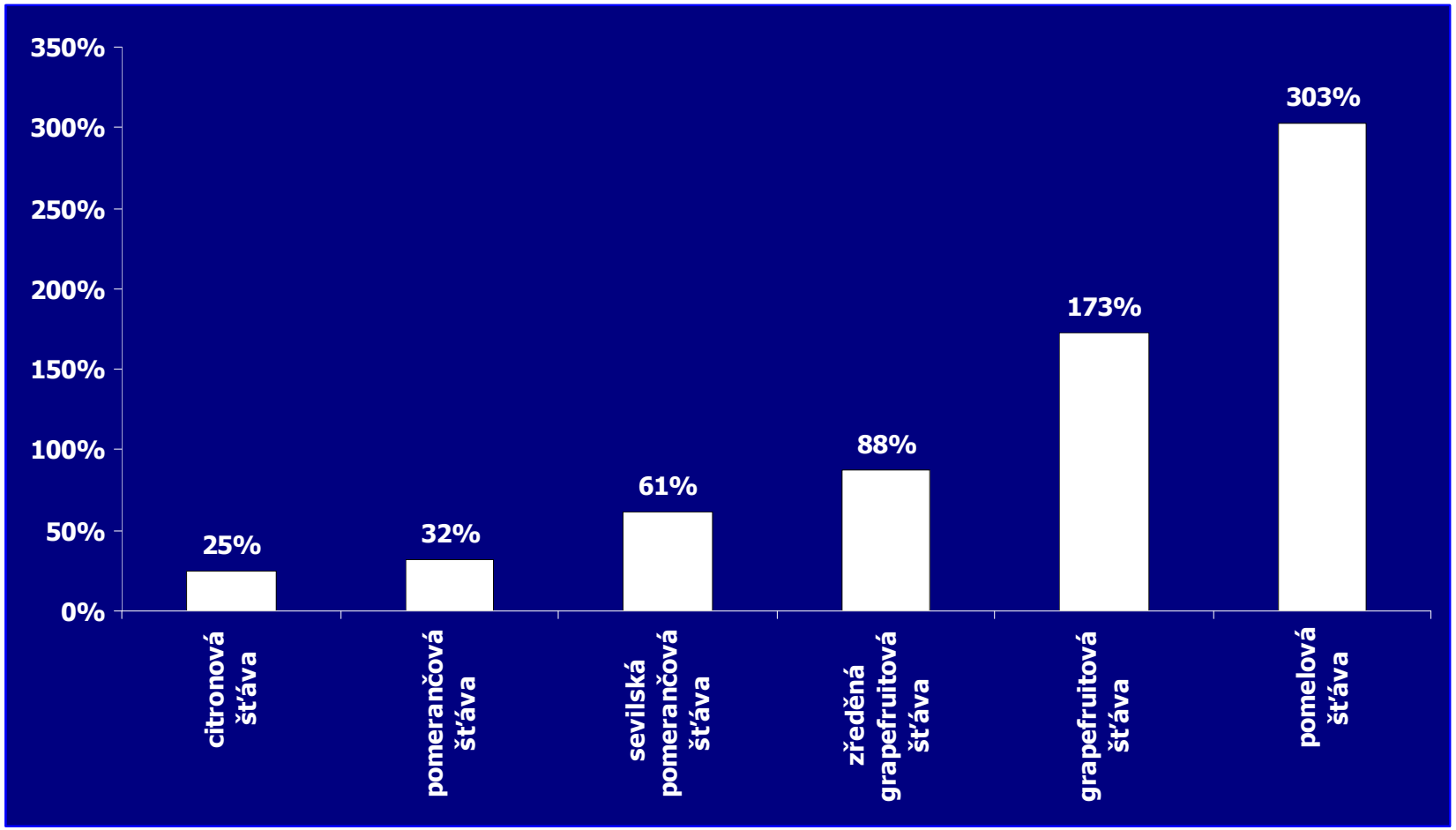
Foods as CYP modulators

- Garlic
- CYP3A4 inducer
- CYP2C9 inhibitor
- P-glycoprotein inducer
- increase in bleeding after warfarin

- Paprica, cauliflower


nárůst
závažnosti
změn

Citrus juice + felodipine



AUC (%)

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Drug interactions in smokers

Influencing the effect of drugs by smoking

- Pharmacodynamic
- mainly nicotine in the CNS and periphery, has sympathomimetic effects (cardiovascular system, reduces insulin sensitivity)
- Pharmacokinetic
- in the absorption phase - nicotine, other products
- in the metabolic phase - especially polycyclic hydrocarbons

Pharmacodynamic interactions of nicotine

- Beta-blockers
- Less decrease in BP and Heart rate
- Benzodiazepines
- Less sedative effect
- Discontinuation of smoking on prolonged use of benzodiazepines may cause depression
- Opioids
- Reduction of analgesia
- Oral Contraceptives
- smoking increases the risk of complications p.o. contraception
- in women over 35 who smoke more than 15 cigarettes a day the risk of death is 19: 100,000 vs. 3: 100,000

Effect of smoking on CYP1A2 induction

- Smokers have 1.5 x increased CYP1A activity compared to non-smokers
- Polycyclic aromatic hydrocarbons cause metabolic induction
- Induction already occurs when smoking 10 cigarettes/day
- Typically, higher dosages of some drugs are required for smokers
- After smoking discontinuation, the enzyme activity is reduced to 7.3x per week
- Interrupting smoking requires doses to reduce
- High risk NÚL after smoking interruption (extrapyramidal symptoms, cramps…)

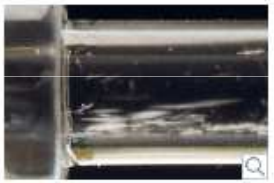
Increased CYP450 activity in smoking

- CYP1A2 amitriptylin, kofein, clozapin, duloxetin, fluvoxamin, haloperidol, imipramin, olanzapin, ondansetron, paracetamol, propranolol, teofylin, warfarin (R-isomer)
- CYP2B6 bupropion, clopidogrel, cyclophosphamid, ifosfamid, methadon, nevirapin

Pharmaceutical drug interactions

Incompatibility

- The incompatibility occurs outside the body, inside the infusion bottles, bags, syringe, or infusion tubes, sometimes visible to the eye.
- **Physical Reaction**
  - In the event of physical reactions to the bath, it is usually a separation or precipitation (eg, dilution of alcoholic solutions) due to a change in the relationship between ionization, non-ionization and solubility.
- **Chemical reaction**
  - Chemical incompatibility means that it is chemically degraded by oxidation, reduction, hydrolysis or decomposition. Chemical reactions can be manifested by turbidity, precipitation, and color changes.
- The result is a reduction in the amount of the medicinal agent or the formation of toxic by-products



Obr. 1a: Chemická precipitace midazolamu (turbidita) a ketaminu (tvorba částic)

Obr. 1b: Fyzikální precipitace midazolamu jako výsledek nepříznivého pH média

Obr. 2a: Fyzikální inkompatibility diazepamu. Obrázek zveřejněn s laskavým svolením F. Schrödera, farmaceuta z Brém v Německu.

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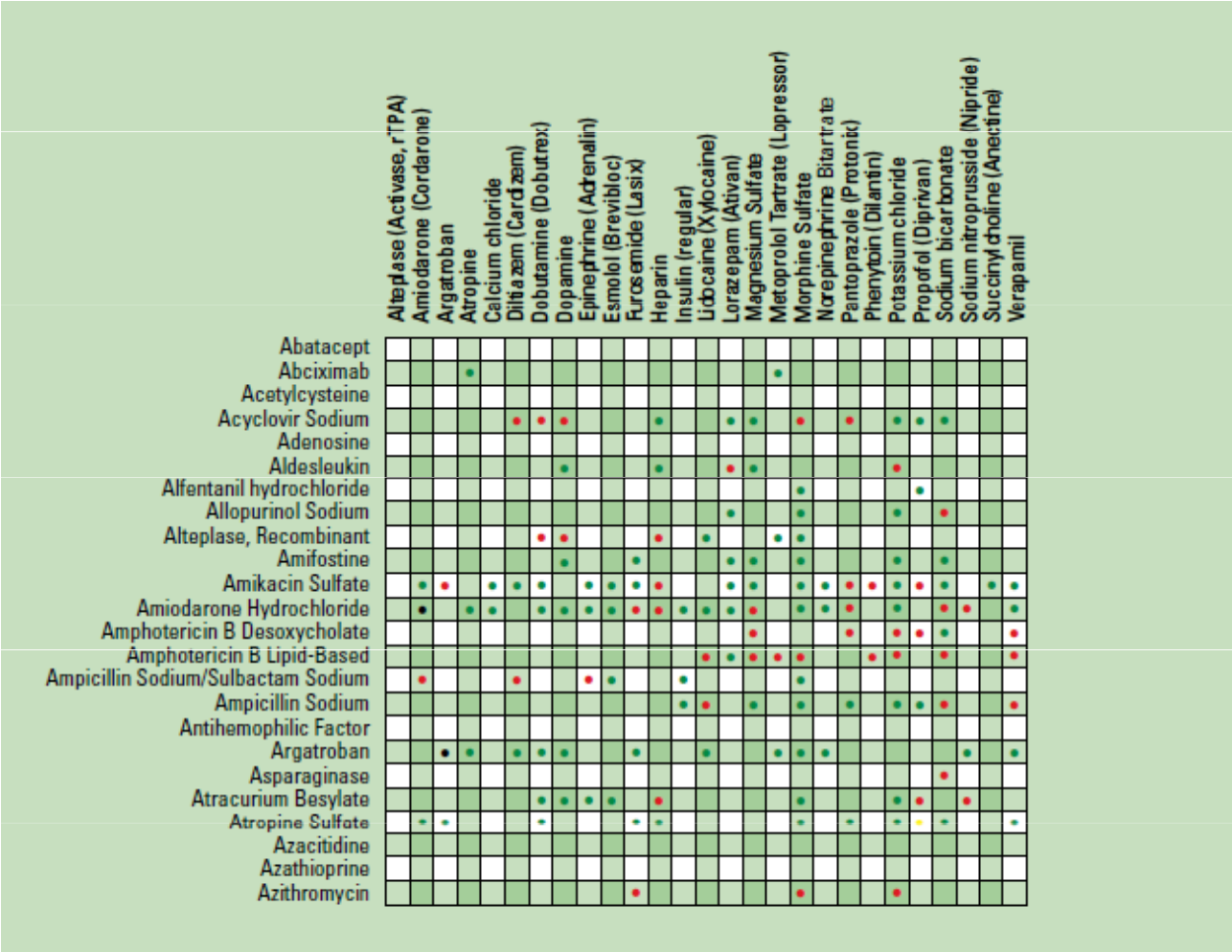
Incompatibility

- Amiodarone diluted in 5% glucose solution meets NE reconstituted in FR - precipitation of amiodarone
  Management - dilute NA to 5% glucose solution

- Octreotide meets in one lumen with parenteral nutrition, octreotide is inactivated
  Management - Separate pathways for parenteral nutrition and octreotide

- Administration of aminoglycosides and beta-lactams meeting in one of the lumens - inactivation of the free -NH2 in the free aminoglycosides and -COOH in beta-lactams
  Management - do not mix in one fluid, split the route of administration, do not give in t the same hour

IV Drug Compatibility Chart



In-vitro: 1-Drug-laboratory tests interaction:

Drug	Laboratory test	Interactions
Cephalosporin	Urinary glucose	False positive result
Cephalosporin	Serum Creatinine	Spurious creatinine levels
Alcohol	γ - glutamyl transpaetidases	Increase in values
Salicylates, Nalidixic acid & Vit C	Urine sugar by Benedict's & Clintest reagents	False positive result
Spironolactone	RIA of Digoxin	Decrease in values of Digoxin
Estrogens	Serum Thyroxine	Increase in levels due to hyperproteinaemia
MAOI's	Urinary VMA levels	Decrease in levels due to reduced metabolism of NE

Recommended links

https://www.drugs.com/drug_interactions.html
https://www.webmd.com/interaction-checker/default.htm
https://reference.medscape.com/drug-interactionchecker
www.arizonacert.org (drug interactions)
www.drug-interactions.com
(P450-mediated drug interactions)
http://www.drugwatch.com/drug-interactions/
http://drugagency.cz/lekove-interakce.php?id=9
http://www.uspharmacist.com

www.QTdrugs.org (drug-induced arrhythmia)
www.C-Path.org (drug development)

Things to remember

- Interactions are easily forgotten when prescribing
- Interactions are difficult to remember
- Pharmacodynamic interactions can often be predicted across drug classes
- Pharmacokinetic interactions can not be predicted – experiments needed
- Many interactions probably remain undescribed – so look out for them
- The chances of interaction are 60 times higher in a patient taking 5 drugs than in one taking 2.

Thank you for attention