Drug interactions

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## Traitement médicamenteux de la confusion aiguë
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Médicaments dans:

choisir un thème

Bon à savoir

- Intervention à partir du 1er juillet 2007 pour certains pansements actifs chez des patients atteints de plaies chroniques [31.07.07]
- Vaccination contre la coqueluche chez les adolescents et les adultes [30.07.07]
- Prévention de la méningite bactérienne [13.07.07]
- Intervention à partir du 1er juillet 2007 pour certaines spécialités analgésiques chez des patients atteints de douleur chronique persistante [29.06.07]
- Maladie de Lyme: vaccination ? [22.06.07]
- La Food and Drug Administration américaine émet des doutes quant à l’innocuité du rimonabant, un médicament contre l’obésité [22.06.07]
- Le statut OMNIO entre en vigueur le 1er juillet 2007

Répertoire

Commenté des Médicaments
Juillet 2007
(prix + remboursement: août)

Parcourir les chapitres

Sélectionner ...

 Chercher par:

nom de spécialité

ABCDEFGHIJKLMNOPQRSTUVWXYZ

principe actif

ABCDEFGHIJKLMNOPQRSTUVWXYZ

Chercher dans le Répertoire

Chercher

Folia

Pharmacotherapeutica

Juillet 2007

Consulter les archives

- Ce mois-ci dans les Folia
  - Articles
    - Prévention et traitement de l’ostéoporose postménopausique
    - Avertissement concernant le risque cardio-vasculaire avec la rosiglitazone
  - En bref
    - Traitement des infections urinaires simples
  - Pharmacovigilance
    - Mesures de précaution lors de l’utilisation de rétinoïdes par des femmes en âge de procréer
- Bon à savoir
  - Deuxième vaccin contre le rotavirus: Rotateq®. Attention: différences avec le Rotarix® concernant la posologie et le coût
  - Discussion concernant l’indication 'énucléaire nocturne chez l’enfant' pour les formes nasales de desmopressine

Chercher dans les Folia

Chercher
Interactions

- Preliminary remarks
- Mechanisms
- The risk situations and risk classes
- The lists: sources of information and their discrepancies
- Some examples for drug classes
- Some examples of clinical consequences
- Conclusions
Interactions : preliminary remarks

-Interactions between drugs, but also between drugs and food, drink, alcohol, herbs ...

-Some effects are wanted (e.g. cardiovascular, oncology, HIV), but often the consequences of an interaction are unwanted

-The effect can be increased (with side-effects) or decreased (with possible loss of efficacy) during or after concomitant use

-The interest should go mainly to drugs with a narrow toxic-therapeutic range or important intrinsic toxicity

-Clinical relevance : severity and frequency
Interactions: mechanisms

- Pharmaceutical interactions
- Pharmacodynamic interactions
- Pharmacokinetic interactions

P.S. Interaction problems are often both pharmacodynamic and pharmacokinetic
The pharmacodynamic interactions

- Occur at the level of the cells (e.g. receptors) or are due to interference with reflex adaptations of the organism (e.g. cardiovascular, central nervous system)

- Often class effect, but ... 

- Often predictable based on the pharmacodynamic effect, but ... 

- More difficult to study than pharmacokinetic interactions and therefore often neglected
The pharmacokinetic interactions

With a *precipitant* drug and an *object* drug

- Absorption
- Distribution
- Renal excretion
- Biotransformation

P.S. Interactions at the level of P-glycoprotein (PgP)
The pharmacokinetic interactions: absorption

- Influence on the absorption rate (with changes in peak concentration which can be relevant) and/or the total absorption (AUC)
- Via an influence on gastric pH or emptying, adsorption, chelation...

P.S. Influences on intestinal first-pass (e.g. grapefruit)
The pharmacokinetic interactions: distribution

- Changes of tissue binding or plasma protein binding
- Changes of plasma protein binding can lead to changes in free fraction, but in vitro experiments tend to overestimate this phenomenon (often high concentrations are tested)
- For a given change in free fraction, there is often less change in free concentration, due to compensatory mechanisms (distribution, elimination)
The pharmacokinetic interactions: renal excretion

- Changes in pH and tubular reabsorption
- Competition for active pumps (e.g. probenecid versus penicillins)
The pharmacokinetic interactions: biotransformation

-Biotransformation takes place mainly in the liver but also elsewhere (e.g. intestinal wall, important for first-pass)

-There is much interest for the cytochrome P450 iso-enzymes
The cytochrome P450 iso-enzymes

- A number of families (> 36 % homology of the aminoacid sequence) e.g. CYP2

- With in each family a number of subfamilies (> 77 % homology) e.g. CYP2D

- With in each subfamily a number of specific enzymes e.g. CYP2D6
# The human cytochrome P450 iso-enzymes

<table>
<thead>
<tr>
<th>FAMILY</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUBFAMILY</td>
<td>A</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>ENZYME</td>
<td>1A1</td>
<td>2A6</td>
<td>2B6</td>
</tr>
<tr>
<td></td>
<td>1A2</td>
<td>2A7</td>
<td>2B7</td>
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<tr>
<td></td>
<td>2A13</td>
<td>3A7</td>
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</table>
The CYP’S : a few comments

-Large interindividual variability (genetic and acquired), with genetic polymorphism for CYP2D6, CYP2C9, CYP2C19

-A drug can be metabolized by one or by several CYP’s

-A drug can inhibit or induce one or several CYP’s

-Drugs (and other substances) can be potent or less potent inhibitors or inducers

P.S. The “important” CYP interactions : how to decide ?
### Principales isoenzymes CYP, et leurs principaux substrats, inhibiteurs et inducteurs: les inhibiteurs et inducteurs les plus puissants sont en gras.

<table>
<thead>
<tr>
<th>Substrats</th>
<th>Inhibiteurs</th>
<th>Inducteurs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CYP1A2</strong></td>
<td>Cimétidine, ciprofloxacine, fluvoxamine, ticlopidine</td>
<td>Barbituriques, carbamazépine, phénytoïne, oméprazole, primidone, rifabutine, rifampicine, tabagisme</td>
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<tr>
<td>Répaglinide, rosiglitazone</td>
<td>Triméthoprime</td>
<td>Rifampicine</td>
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<td>Anti-inflammatoires non stéroïdiens, fluvastatine, phénytoïne, S-warfarine</td>
<td>Amiodarone, cimétidine, fluconazole, fluvoxamine, isoniazide, miconazole, sulfaméthoxazole, phénylbutazone, voriconazole, zafirlukast</td>
<td>Barbituriques, carbamazépine, phénytoïne, primidone, rifampicine, ritonavir</td>
</tr>
<tr>
<td><strong>CYP2C8</strong></td>
<td>Amiodarone, cimétidine, fluconazole, fluvoxamine, isoniazide, miconazole, sulfaméthoxazole, phénylbutazone, voriconazole, zafirlukast</td>
<td>Phénoobarbital, phénytoïne</td>
</tr>
<tr>
<td>Citalopram, clomipramine, diazépam, ésomeprazole, Lansoprazole, oméprazole, pantoprazole, phénytoïne, proguanil</td>
<td>Cimétidine, ésomeprazole, fluoxétine, fluvoxamine, oméprazole, ticlopidine</td>
<td>Inconnu</td>
</tr>
<tr>
<td><strong>CYP2C9</strong></td>
<td>Amiodarone, bupropion, cimétidine, duloxétine, fluoxétine, paroxépine, propafénone, quinidine, ritonavir, terbinafine</td>
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<tr>
<td><strong>CYP2D6</strong></td>
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<tr>
<td>— Antiarthymiques: flécaïnide, propafénone, mexilétine</td>
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<tr>
<td>— Antidépresseurs: amitriptyline, clomipramine, désipramine, duloxétine, imipramine, nortriptyline, paroxépine, venlafaxine</td>
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<tr>
<td>— Antipsychotiques: aripiprazole, halopéridol, rispendone, zuclopenthixol</td>
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<td>— β-bloquants: métoprolol, timolol</td>
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<tr>
<td>— Divers: codéine, dextrométhorhaphne, tramadol</td>
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</tr>
<tr>
<td><strong>CYP2C19</strong></td>
<td>Amiodarone, cimétidine, ciprofloxacine, clarithromycine, clindamycine, érythromycine, fluconazole, les inhibiteurs des protéases, itraconazole, kétoconazole, névirapine</td>
<td></td>
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<tr>
<td><strong>CYP3A4</strong></td>
<td>Benzodiazépines: alprazolam, diazépam, midazolam, triazolam</td>
<td></td>
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<tr>
<td>— Antagonistes du calcium: diltiazem, vérapamil</td>
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<tr>
<td>— Statines: atorvastatine, simvastatine</td>
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</tr>
<tr>
<td>— Divers: alfentanil, aprépitant, aripiprazole, budésone, buspirone, carbamazépine, ciclosporine, cisapride, dexaméthasone, dihydroyergotamine, éthritapant, ergotamine, étthylenestradiol, évèrolimus, halopéridol, imatinib, irinotécan, méthadone, méthylprednisolone, pimozone, quetiapine, réboxétine, sibutramine, sildénaïl, sirolimus, solifénaïne, tacrolimus, tadalafil, théophylline, tramadol, trazodon, vardénaline, vincristine</td>
<td></td>
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</table>
The CYP’s: “important” inducers and inhibitors

CYP1A2  *Inhib.*: fluvoxamine
*Inducers*: barbiturates, carbamazepine, phenytoïn, rifampicin

CYP2C9  *Inhib.*: miconazol, phenylbutazon
*Inducers*: barbiturates, carbamazepine, phenytoïn, rifampicin

CYP2C19  *Inhib.*: fluvoxamine

CYP2D6  *Inhib.*: bupropion, fluoxetine, paroxetine, propafenone, quinidine, ritonavir, terbinafine

CYP3A4  *Inhib.*: clarithromycin, erythromycin, grapefruit, itraconazol, ketoconazol, protease-inhibitors, voriconazol
*Inducers*: carbamazepine, rifampicin, St.John’s Wort
Interactions at the level of the CYP’s

- The concentrations of the object drug can be changed by CYP induction or inhibition

- The change is mainly important when the object drug is metabolized by only one CYP, and the precipitant drug is a potent inducer or inhibitor

- The interaction often takes place at the level of gut or liver first-pass
Interactions at the level of P-glycoprotein (PgP)

-PgP is an active efflux pump, localized in plasma membranes (gut, liver, kidney, brain ...)

-There is a marked overlap between substrates, inducers and inhibitors for CYP3A4, and those for PgP (with exceptions, e.g. digoxin)

-Substrates: anti-cancer drugs, calcium entry blockers, digoxin, immunomodulators, HIV-protease inhibitors ...

-Inhibitors: erythromycin, ketoconazol, quinidine, verapamil, ciclosporin, (grapefruit juice ?)...

-Inductors: rifampicin, phenobarbital, St. John’s Wort
PgP IN GI TRACT

IMPORTANT INFLUENCE ON BIOAVAILABILITY OF DRUGS

GUT LUMEN

DRUG → metabolites

ENTEROCYTE

DRUG → CYP3A4 → metabolites

PORTAL BLOOD

metabolites → DRUG → metabolites
DIGOXINE-RIFAMPICINE INTERACTIE

DIGOXINE PER OS

DIGOXINE INTRAVENEUS

Greiner et al., J Clin Invest 104:147-153, 1999
The risk situations for interactions

- Polymedication
- Old age
- Presence of renal failure, heart failure (e.g. for NSAID’s and ACE-inhibitors), asthma
- Drugs undergoing marked first-pass (gut, liver)
- Drugs with narrow therapeutic-toxic margin
- Drugs with high intrinsic toxicity
- Use of high doses
- Certain classes of drugs
Drug classes with high risk for interactions

- Anti-arrhythmics
- Anticoagulants
- Anticonceptives
- Anti-epileptic drugs
- H1-antihistaminics
- Anti-HIV drugs
- Antimycotic drugs

- Beta-blockers
- Digitalis
- Immunosuppressants
- NSAID’s
- Statins
- Triptans

...
The sources of information

- Summary of product characteristics
- Martindale
- Stockley’s Drug Interactions
- Hansten and Horn: The Top 100 drug interactions
- Meyler’s Side Effects of Drugs
- La Revue Prescrire, suppl.: “Interactions médicamenteuses, comprendre et décider”
- http://afssaps.sante
- British National Formulary
  www.bnf.org/bnf/bnf/current/openat/index.htm

P.S. The discrepancies between sources
The Top 100 Drug Interactions

A Guide to Patient Management

2005 Edition

Philip D. Hansten, Pharm.D.
Professor Emeritus of Pharmacy
University of Washington
Seattle, Washington

John R. Horn, Pharm.D.
Professor of Pharmacy
University of Washington
Seattle, Washington
ÉVITER LES EFFETS INDÉSIRABLES
PAR INTERACTIONS MÉDICAMENTEUSES
COMPRENDRE ET DÉCIDER

LE GUIDE 2007
Drug interactions sources: the discrepancies


“There is a lack of consistency in the inclusion and grading of drug interactions of major significance for 50 drugs across the four drug compendia examined. This may reflect the lack of standardization of the terminology used to classify drug interactions and the lack of good epidemiological evidence on which to base the assessment of the clinical relevance of drug interactions.”
Drug interactions sources: the discrepancies

The lack of good evidence

- Difficulties: large number of possible combinations, intra-individual variability, in vitro versus in vivo, doses used, individual drug versus drug class, case-reports, unfrequent events ...

- Information sources should indicate the quality of the evidence, e.g. as proposed by Aronson, Br J Clin Pharmacol 2007;63:637-9:
  A: anecdotes
  D: data from laboratory experiments or extrapolated from theory
  R: randomised trials or observational studies

But: quality of the evidence!
Drug interactions sources: the discrepancies
Problems of terminology

Hansten and Horn 2005

Class 1: Avoid Combination (*Risk of combination outweighs benefit*)

Class 2: Usually Avoid Combination (*Use only under special circumstances*)

Class 3: Minimize Risk (*Assess risk and take one or more of the following actions if needed*)

Class 4: No Special Precautions (*Risk of adverse outcome appears small*)

Class 5: Ignore (*Evidence suggests that the drugs do not interact*)

(cont.)
Drug interactions sources : the discrepancies
Problems of terminology (cont.)

-The decision to allocate a certain interaction to one of
the Hansten and Horn classes is in most cases
arbitrary

-There are a few examples of true class 1 interactions
(to be avoided in all circumstances) but for many of
the interactions mentioned by Hansten and Horn, it is
difficult to decide between classes 1 and 2, between
classes 2 and 3, between classes 3 and 4
Interactions : some examples for drug classes

-Antidepressant drugs
-Coumarine anticoagulants
-Statins
-NSAID’s
-Oral contraceptives
-Anti-Alzheimer drugs

P.S. : - alcohol
    - grapefruit
    - herbs (e.g. St. John’s Wort)
Antidepressant drugs

- The serotonin syndrome (cfr. below)

- First and second generation antidepressants
  ↓ effect of central antihypertensives,
  ↑ sedation, anticholinergic effects by other drugs
  ↑ or ↓ biotransformation (CYP’s)

- SSRI’s
  • interactions via CYP’s
    fluoxetine: inhibits 2D6, 2C19, 3A4
    fluvoxamine: inhibits 1A2, 2C9, 3A4
    paroxetine: inhibits 2B6
    citalopram, escitalopram, sertraline: no?
  • increased risk of GI bleeding with NSAID’s (and ASA)

- St. John’s Wort: induction of CYP3A4 (and PgP?)
Coumarine anticoagulants

- The pharmacodynamic interactions with other drugs interfering with coagulation

- The pharmacokinetic interactions (mainly via CYP2C9) : certainly for warfarine, possibly also for acenocoumarol; less for fenprocoumon

P.S. With increased (bleeding) or decreased (lack of efficacy) effect : mainly at the moment of starting or stopping the precipitant drug
Statins

- The statins (and also ezetimibe) are toxic for the muscle cells, with risk of myalgia and rhabdomyolysis (risk factors: high doses, renal failure, alcohol use, old age)

- More risk due to interactions
  . Pharmacodynamic: + fibrates, + ezetimibe
  . Pharmacokinetic:
    atorvastatine and simvastatine: ↑ conc. with CYP3A4-inhibitors
    fluvastatine ↑ conc. with CYP2C9-inhibitors
  . Unknown mechanism: all statins + ciclosporine
SIMVASTATINE-ITRACONAZOL INTERACTIE

HMG-CoA reductase inhibitors (ng eq/ml)

Time (hr)

with itraconazole

with placebo

Rhabdomyolysis by simvastatin
(Belgian Centre for Pharmacovigilance)

Lady 87 years
-Since one year simvastatin 40 mg per day
-During one week itraconazole 200 mg per day for intertrigo
-Two and a half weeks after stopping itraconazole: rhabdomyolysis and acute renal failure, and death

High dose of simvastatin, CYP3A4 inhibition by itraconazol, in the presence of decreased renal function (age !)

P.S. Rational prescribing ?
Non-steroidal anti-inflammatory drugs

Pharmacokinetic interactions
- Displacement of other drugs (e.g. coumarin anticoagulants from plasma proteins) ?
- Decreased excretion of lithium

Pharmacodynamic interactions
- Increased risk of gastric bleeding when given with glucocorticoids
- Increased risk of GI bleeding with SSRI’s
- Less effect of diuretics and antihypertensives
- ↑ nefrotoxicity of ciclosporine
- ↑ hyperkalaemia (cfr.)
- ↓ cardioprotective effect of aspirine ?

P.S. Loss of the GI advantage of COX-2-NSAID’s by low dose aspirin ?
Concomitant use of ibuprofen and aspirin
(FDA information for health care professionals)

• Patients who use immediate release aspirin (not enteric coated) and take a single dose of ibuprofen 400 mg should dose the ibuprofen at least 30 minutes or longer of aspirin’s effect.

• Recommendations about the timing of concomitant use of ibuprofen and enteric-coated low dose aspirin cannot be made based upon available data.

• Other nonselective OTC NSAIDs should be viewed as having the potential to interfere with the antiplatelet effect of low-dose aspirin unless proven otherwise.
Interactions with loss of anticonceptive effect of oral estroprogestative contraceptives

- Induction of CYP3A4 by barbiturates, carbamazepine and oxcarbazepine, felbamate, fenyturide, fenylbutazon, fenytoïne, griseofulvine, primidon, rifampicin en rifabutin, ritonavir, topiramate ...
  Also by St. John’s Wort (breakthrough bleeding; pregnancy ?)

- Antibiotics other than rifampicin and rifabutin

P.S. Difficulty of proving that pill failure is due to an interaction, and not e.g. to lack of compliance
Interactions with cholinesterase-inhibitors as anti-Alzheimer drugs

- Pharmacodynamic
  . with drugs with an anticholinergic effect (cognitive deterioration and urinary problems)
  . with neuroleptics (extrapyramidal symptoms and increased mortality)
  . with cardiac drugs (bradycardia, conduction disorders)

- Pharmacokinetic
  . rivastigmine: no
  . donepezil and galantamine: more unwanted effects when CYP3A4-inhibitors or CYP2D6-inhibitors are associated

P.S. How to recognize such side-effects in an elderly population?
Interactions with alcohol

Pharmacodynamic interactions
. with drugs with effects on the CNS
. with hypoglykemic drugs, antihypertensives, antithrombotic drugs
. with paracetamol in overdose

Pharmacokinetic interactions
. as object drug: increased alcohol concentration with i.a. cimetidine; disulfiram reactions
. as precipitant drug: with acute use inhibition of drug biotransformation; with chronic use enzyme induction

P.S. Often pharmacodynamic + pharmacokinetic
**Interactions with grapefruit (juice)**

- Mainly inhibition of CYP3A4 in the gut wall (first-pass, not hepatic)
- Leads to increased concentrations of the object drugs
- Active substance?
- How much juice?
- Composition of the juice?
- For how long is the interaction present? (long)
- Substrates: see following slide

P.S.- Can this be used to decrease the dose of drugs which are difficult to manufacture?
- The interaction does not occur with other juices
Interactions with grapefruit (juice)

(continued)

Important substrates for CYP3A4

- Calcium antagonists
- Benzodiazepines with first pass (triazolam, diazepam)
- Psychotropic agents (buspirone, carbamazepine)
- Statins (simvastatine, lovastatine, atorvastatine)
- Phosphodiesterase type 5-inhibitors (e.g. Viagra®)
Interactions drugs-herbs

- Certainly not unfrequent i.a. ginkgo biloba, Allium sativum, ginseng, senna, cascara, cranberry juice, St. John’s Wort (see La Revue Prescrire 2007, vol. 286, numéro spécial “Bien utiliser les plantes en situations de soins”)

- Special attention for St. John’s Wort (Hypericum perforatum):
  - Serotonin syndrome (cfr)
  - Induces CYP3A4, possibly also P-glycoproteïn
INDINAVIR EN St-JANSKRUID

Mean concentration-time of indinavir alone (solid line) and with concomitant St John’s wort (dotted line)

Piscitelli et al., The Lancet 355:547, 2000
Interactions: some examples of clinical consequences

- Cardiovascular or central depression with numerous combinations of drugs
- QT-prolongation and torsades de pointes
- Serotonin syndrome
- Hyperkalaemia
QT-prolongation

- QT-prolongation can cause torsades de pointes and death

- Which drugs can prolong the QT-interval?
  i.a. class I and III-anti-arrhythmics, cisapride, ketanserin, some neuroleptics, amfotericine B, pentamidine, erythromycine intravenously (and possibly also clarithromycine), telithromycine, levofloxacine and moxifloxacine, methadon

P.S. The H1-antihistaminics other than terfenadine (Triludan) and astemizol (Hismanal)?
QT-prolongation : risk situations for “torsades de pointes”

- Bradycardia, hypokalaemia, congenital QT-prolongation, overdose, cardiac disease ...
- Interactions
  - Combination of drugs which prolong the QT-interval
  - Combination of a drug which prolongs the QT-interval + an inhibitor of its metabolism (important e.g. for cisapride, erythromycine intravenously)
  - Combination of a drug which prolongs the QT-interval + a potassium losing diuretic
A case report

A 20 year old lady consults her general practitioner for recurrent vaginal mycosis. R/itraconazole
Before leaving, she mentions an itching skin lesion R/terfenadine (an H$_1$-antihistaminic)

Two days later, she is found death in her bed

Probably torsades de pointes : terfenadine (which is cardiotoxic) is a pro-drug which is in first-pass after oral administration almost completely metabolized (CYP3A4) to the active fexofenadine, but in overdose or if CYP3A4 is inhibited (e.g. by itraconazole), terfenadine reaches the systemic circulation
The serotonin syndrome

- Symptoms: confusion, hyperthermia, myoclonus, salivation, tremor ... (difficult to differentiate from delirium and from malignant neuroleptic syndrome)

- Can occur with drugs which increase the serotonin concentration at the level of the receptors (tryptophan, MAO-inhibitors, amphetamines, SSRI’s, sibutramine, TCA’s, lithium, St. John’s Wort...)

- Usually only seen when several of these drugs are given concomitantly

(Boyler and Shannon, NEJM 2005, vol. 352, pp. 1112-1120)
Hyperkalaemia

- Consequences: heart, striated muscle ...
- Mainly in patients with renal failure (e.g. elderly)
- More risks when several drugs are given concomitantly
  - Potassium supplements, potassium sparing diuretics
  - ACE-inhibitors, sartans
  - NSAID’s
  - Ciclosporine, tacrolimus
  - Heparin
  - Erythropoietine

P.S. Spironolacton (> 50 mg) in association with ACE-inhibitors or sartans for treatment of cardiac failure (BMJ 2003, vol. 327, pp. 147-49)
Conclusions

- Evidence about interactions is often lacking
- The terminology for communication is often unclear
- Not all interactions deserve the same attention (severity, frequency)
- Knowing the mechanism is helpful
- Avoid polypharmacy
- Monitoring the patient is important
- Where to find the correct information at the moment of prescription? Prescription aids?