The role of drug-drug interactions in the clinical practice

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„Primum nil nocere!”
Iatrogenic

"iatric", originally greek word, the meaning: science of medicine "iatrogenic", meaning in the everyday language: an unintentional harm caused by some medical activity, a curative treatment by medicaments, by surgery...
In the background of iatrogenic events, which occur as the consequence of curative medical treatment can be adverse drug event, (ADE), and/or adverse drug reaction, (ADR)
ADVERS DRUG REACTION (ADR)

Generally known side effects of the drugs
ADVERSE DRUG EVENT (ADE)

„an unintended injury caused by medical management rather than a disease process, resulting in death, life threatening illness, disability at the time of discharge, admission to hospital or prolongation of hospital stay”
In the USA, 10% of the hospitalisation occurred because of ADE, and there was registered 140,000 death caused by ADE. Analysing the exact results, it came out, that 28% of these ADEs might have been avoided. The rate of the drug-drug interaction in the ADEs was between 5-80%. Wester et al. have screened the general population and they have found, that ADR was responsible of 3% of death. It means, that the ADR is the 7-th most frequent cause of death in Sweden.
Emergency hospitalization for ADE in older americans

- Surveillance between 2007-2009
- On the basis of 5077 cases identified – 99682 emergency hospitalisation was estimated
- Patients age was 65 years or older
- Half of these hospitalisation affected 80 years of age or older
- Nearly two thirds of hospitalisations were due to unintentional overdoses
- The implicated medications: warfarin (33%) insulin(14%), oral antiplatelet agents (13%), oral hypoglycemic agents (11%)

FACTS

„30-50 % of the pharmacies gave out drugs, which as applied concomitant medication, can cause clinically significant, life threatening interaction without any comment”

No the patient, no the doctor who prescribed the drugs have been warned.

The investigation was done in several big cities of the USA in 1996. MD.Johnson et al. Clinically important drug-drug interactions
DEFINITIONS

Clinical pharmacology
- Investigates the interaction of the drugs (medicines) and the human organism.

The main questions are:
- What the body does to a drug? (pharmacokinetics)
- What a drug does to the body? (pharmacodynamics)
DEFINITIONS

**Drug:** generally a small molecular weight material, which is given to the patient purposely to treat his/her illness. It has no other role in the body.

**Pharmacokinetics** Absorption, Distribution, Metabolism and Excretion---ADME

**Elimination:** Metabolism and Excretion

**Pharmacodynamics** the mode of action of the drug. It can influence different cells, receptors, enzimes, ion channels ect. of the organism
NEW DRUG DEVELOPMENT

Discovery

Preclinical studies
animal-experiments: pharmacology, toxicology

HUMAN studies

• Exploratory: Phase I-II studies
• Confirmatory: Phase III studies
• Observational: Phase IV studies
THE MAIN QUESTIONS

Phase I

Is it safe?

10-30 healthy volunteers
Phase II

Is it EFFECTIVE?

100-300 volunteers- patients
Phase III

Is it effective in double blind conditions?

400-4000 volunteers-patients
Phase I V

What is happening in the real world?
The patients' response to drugs is very variable. The reasons are diverse and complex:

- Genetic polymorphisms
- Intrinsic factors (genetic, body weight, body height, race, receptor sensitivity, sex)
- Extrinsic factors (alcohol, smoking, diet, climate, culture, educational status, drug adherence, illnesses)
DRUGS

In the everyday life very frequently occurs that the patients take not only one drug. The more drug is taken by the patients the more possibility of drug-drug interaction.

**Pharmacodynamic and pharmacokinetic interactions can occur between the drugs.**
**DRUG-DRUG INTERACTION**

*Five drug* (n) taken together results in mathematically potential interaction ten. (using this equation: \( N = \frac{n!}{2!(n-2)!} \)  
\( N = \frac{1 \times 2 \times 3 \times 4 \times 5}{1 \times 2 \times (1 \times 2 \times 3)} = 10 \)

*Ten drug* taken together results in **45 interactions!!!**
Factors influencing drug-drug interaction

- activity of metabolism
- actual illness
- diet
- age
- race
- dose of the applied drug
- dose-effect curve (stepness)
- narrow therapeutic range
- liver transplantation
The result of the interaction

- Additional
- Potentiational
- Inhibition

The result of interaction can be useful or harmful
Interaction can occur between:

- Two or more drugs
- Drug and food
- Drug and alcohol, nicotine, beverages
- Drug and cosmetics
- Drug and plant protecting agents
- Drug and diagnostic materials (contrast materials)
Drug elimination

- Patient’s response to drugs varies widely
- The organisms have to get rid of drugs
- Metabolism and/or excretion
- Individual differences
- In the background: polymorphisms of cytochrome P 450 enzymes
Drug metabolism occurs mainly in the liver

The most frequent reaction of biotransformation: **oxidation**, catalysed mainly by cytochrome P450 enzymes.

These enzymes are not specific for substrates, they oxidise several different drugs, and endogenous materials.
CYP 450 enzymes oxidise

- cholesterol
- Steroids
- prostacyclin
- tromboxan A2
Six isoenzymes are responsible for 90% of drug-metabolisation:

- CYP1A2
- CYP2C9
- CYP2C19
- CYP2D6
- CYP3A4
- CYP3A5

Extremely important: CYP3A
CYP3A izoenzymes

CYP3A (40-60 % of liver isoenzymes) group is responsible for the most P450 drug-drug interaction
INDUCTION-INHIBITION

The enzym induction and inhibition by drugs can influence the effects of other drugs, which are also metabolised by the same enzym.

The induction an enzym can decrease the effect of an other drug which is also metabolised by the same enzym.

The inhibition an enzym can increase the effect of an other drug which is also metabolised by the same enzym.
IMPORTANT!!!

Drugs, herbs, foods, chronic alcohol consumption, grapefruit-juice, benzpiren (contained by cigarette smoke) influence the activity of cytochrome P450 enzymes, by inhibition and/or induction, taking part in the drug-drug, and drug-other material interaction.
SMOKING-ALCOHOLISM

Drug metabolism can be increased, (effect decreased) because of the benzpiren and alcohol can induce the enzymes of cytochrome P450 family
Bioflavonoids inhibit the CYP1A2, CYP3A isoenzymes, which take part in the metabolism of some beta blockers, fluvastatin, dihydropiridin-type calcium channel blockers.

The result: increasing effect of these drugs
IMPORTANT!!!

- Enzymes of the drug metabolism are not specific.
- There is competition between substrates for the same enzyme, and reversible or irreversible competitive inhibition can occur.
The irreversible enzyme inhibition is responsible more frequently for life-threatening drug-drug interaction.
Drugs in the everyday practice having definitive enzym-inhibitory activity

<table>
<thead>
<tr>
<th>Amiodarone</th>
<th>Diltiazem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinidine</td>
<td>Verapamil</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Irbesartan</td>
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<tr>
<td>Ciprofloxacin</td>
<td>Losartan</td>
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<tr>
<td>Fluvoxamine</td>
<td>Omeprazol</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Lanzoprazol</td>
</tr>
<tr>
<td>Fluconazol</td>
<td>Haloperidol</td>
</tr>
<tr>
<td>Metronidazol</td>
<td>anti-HIV agents</td>
</tr>
<tr>
<td>Ritonavír</td>
<td>Ticlopidin</td>
</tr>
<tr>
<td>trimethoprim/sulfamethoxazol</td>
<td>Erythromycin</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Iatroconazol</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Ketokonazol</td>
</tr>
<tr>
<td>Clarithromycine</td>
<td>+ grépfruit-juice</td>
</tr>
</tbody>
</table>
Drugs in the everyday practice having definitive enzym-induction

- Carbamazepine
- Phenobarbital
- Rifampicin
- Phenytoin
- Omeprazol
- Lanzoprazol
- Dexametazon
- haloperidol,
- benzpiren
- Well Roasted, grilled meats
- cabbageas
- Herb (hypericum)
What can we do?

- Avoid polypragmasy!
- Pay attention to possible drug-drug interactions!
- Avoid dangerous drug combinations, choose alternative treatment
- Measuring the drug plasma-level
- Ask the patients about consumption of herbs, alternative medicines, alcohol, smoking!
Do not worry! The best things used to happen, when you would not wait it.
Non-wanted pregnancy due to drug interaction

- Antiepileptics (fenitoin, pirimidon, carbamazepin), fenobarbital, rifampicin, herbs (hypericum) induce the CYP3A4 isoenzyme, provoking the faster elimination of anticoncipients, resulting in decrease of effect.

- Neuroleptics, sedatives, antibiotics also can cause decrease in effect

In Germany, 50,000 conceptions have occurred per year, meanwhile the mother took anticoncipients.

Berg, C: [www.pharmazeutische-zeitung.de/online](http://www.pharmazeutische-zeitung.de/online) (200-17) 2006.08.15.08:47
Danger of bleeding!

**Drug increasing the effect of warfarin:**
- paracetamol, amiodarone, anabolic steroids, cimetidine, ciprofloxacin, disulfiram, erythromycin, fluconazol, isoniazid, vaccination against influenza, iatroconazol, lovastatin, metronidazol, miconazol, non-steroidal antiinflammatory drugs, norfloxacin, ofloxacin, omeprazol, phenytoin, propafenon, propranolol, salicylic acid, tamoxifen, tetracyclin, thyroxin, trimethoprim/sulfamethoxazol

**Herbs:** sage (salvia), harpagophytum procumbens, angelica archangelica, garlic, ginkgo biloba, vitamin E
Danger of thrombo-embolism

Drugs decreasing the effect of warfarin:
- azathioprin, barbiturates, carbamazepine,
- cholestyramin, cyclosporin, dicloxacillin,
- griseofulvin, nafcillin, rifampicin, sucralfate,
- trazodone

- foods: avocado, majonaise, mustards,
  vegetables containing high amount of kalium,
  (lettuce, cabbages, cauliflowers, brussels sprouts,
  parsley, spinach)

- herbs: coenzyme Q 10, ginseng, hypericum
Patients treated by analgetics

**NSAID-s**: decrease the effect of antihypertensives

**NSAID-s**: increased nephrotoxicity of cyclosporin

**Drugs increasing the hepatotoxicity of Paracetamol**: carbamazepin, phenytoin, barbiturátok, rifampicin, alkohol, sulfinpyrazon, isoniazid, zidovudin
Long QT syndrom, life-threatening torsades de pointes

Macrolids antibiotics (erythromycin, clarithromycin, roxithromycin) and moxifloxacin giving together with IA and III group antiarrhythmics, some antipsychotics, antihistamins, agents provoking hypokalemia are able to make longer the QT distance
Drugs provoking long QT syndrome and torsades de pointes

- Amiodaron
- Budipin
- Chloroquin
- Clarithromycin
- Disopyramide
- Droperidol
- Erythromycin
- Haloperidol
- Methadon
- Pimozid
- Procainamid
- Quinidin
- Terfenadin
- Thioridazin
Macrolids (erythromycin, clarithromycin) inhibit other drugs metabolism, resulting in increasing effects and side effects

- Statins: rhabdomyolysis risk increases
- Ciclosporin, tacrolimus: nefrotoxic effect increases
- Calcium-channel blockers: hypotension, oedema, flush more frequent
- Theophyllin: tachycardia more impressive
- Digitalis: bradycardia more pronounced
- Clozapin, buspiron, midazolam: sedative effect increases
- Midazolam: depression of breathing more pronounced
- Warfarin: danger of bleeding increases
Patients taking antidiabetics

- Metformin: contrast material in imaging techniques, renal elimination decreases, risk of renal failure increases
- 48 hours before and after the investigation we have to stop the metformin treatment
CASE I

77 years old male patient

History:
about 10 years hypertension
ischemic heart disease
diabetes mellitus type 2
hyperuricaemia
renal insufficiency

Actual complains: bad general feeling, weakness, worsening parameters of renal function
The treatment of the patient

- lisinopril + amlodipin 1 tabl.
- spironolacton – 1x 25 mg
- carvedilol – 2x12,5 mg
- indapamid – 1 tabl.
- allopurinol – 2x300 mg
- acetylsalicilsav – 100mg
- atorvastatin – 10 mg 1x

Before one week of admission to the hospital, other drugs were added to his prerevious therapy by GP
- lisinopril –1 tabl.
- furosemid + kálium – 2x1 tabl
- spironolacton – 2x25 mg
Patient's parameters

- Blood pressure: 100/60 Hgmm
- seK: 6,5 mmol/l
- Serum creatinine: 231 µmol/l
- GFR: 24 ml/min/1.73 m²

Previous results
- 115-140 µmol/l serum creatinine
- 4,7-5,0 mmol/l serum potassium
What happened with the patient? Farmakodinamic interaction

- Dysspnea and pitting oedema – new complaints

- GP added to the previous therapy:
  - lisinopril
  - furosemid + kálium
  - spironolacton

- The renal insufficiency was known previously

- Higher dose diuretics caused hypovolemia, increasing this way the effect of increased dose ACE inhibitor resulting in hypotension

- The hypotension caused the worsening of renal function

- ACE-inhibitor, beta-blocker and potassium supply + potassium sparing diuretic (spironolacton) together with worsened renal function can be responsible for the hyperkalemia

Treatment: stop antihypertensives, diuretic, fluid supply
CASE II

- 83 years old female
- History: known hypertension (22 y), IHD (11 y), mild azotemia, diabetes mellitus type2, hyperuricaemia, hypercholesterolaemia, knee-arthrosis (7 y)
- Actual complains: pitting edema, dyspnea
- Diagnosis: heart failure, atrial fibrillation
- Treatment: (previously) perindopril, indapamid, metformin, allopurinol, atorvastatin, some times diclofenac, actually enoxaparin was added, and later acenocumarol
- After 20 days she left the hospital
CASE II

After one week she presented herself again, because of pain and edema in the left lower extremity.

The INR > 6

Duplex ultrasound investigation revealed a inter-tissue bleeding (big hematoma) in the lower extremity.
What happened with the patients?

- The advised dose of statin was 10 mg atorvastatin.
- But she has at home only simvastatin 20 mg, and took it, she switched the previous therapy.
- Beside of this, she had pain in her knee, and took several times diclofenac too.
Screening

- Serum potassium ≥ 6 mmol/l
- INR ≥ 4.0
DIPS (Drug Interaction Probability Scale)

1: Van korábbi hitelt érdemlő cikk az interakcióról emberi vonatkozásban?
2: A megfigyelt interakció összhangban van a hozzáadott gyógyszer ismert interaktív tulajdonságaival?
3: A megfigyelt interakció összhangban van a vizsgált gyógyszer ismert interaktív tulajdonságaival?
4: Az eset összhangban van az interakció ismert vagy feltételezett idejével (kezdet és/vagy vég)?
5: A vizsgált gyógyszer változatlansága mellett a hozzáadott szer változtatásával megszűnik az interakció?
6: Megismétlődött az interakció, amikor a hozzáadott gyógyszert ismételten beadjuk a folyamatosan alkalmazott vizsgált szer mellé?
7: Van más elfogadható oka az esetnek? (igen=-1)
8: A vizsgált gyógyszer koncentrációja következetesen kimutatható volt a vérben vagy más testnedvben az interakció során?
9: Megerősítésre került a gyógyszer interakció valamely más módon? (EKG)
10: Az interakció fokozódott a hozzáadott gyógyszer dózisának növelésével, vagy csökkent a dózis csökkentésével?

≥ 9: definitive
5-8: probable
1-4: possible
<1: not possible
Results: patients with hyperkalemia

Patient's number: 4261
male:female=1:1.15

seKalium ≥ 6: 106 case
male:female=1.5:1

2,5%
Side effect

31 case
male:female=1,6:1

0,7% of all hospitalised patients

Se $K^+ \geq 6$: **29% of hyperkalemic patients**
Using DIPS- probability of drug-drug interaction

31 side effects-16 cases due to drug-drug interaction

male:female=1.3:1

0.4% of all hospitalised patients

15% of all hyperkalemic patients

51.6% of drug side effects
Drugs taking part in the interaction

**Spironolacton + ACEI: 13 cases**
- ramipril: 8
- enalapril: 3
- perindopril: 2

**+ β-blocker: 8 cases**
- bisoprolol: 4
- metoprolol: 4

**+ β-blockeró + KCl: 4 cases**

**+ARB: 1 case**

Ø Spironolacton + ACEI: 3 cases
- KCl + ramipril + bisoprolol
- KCl + enalapril + ramipril + atenolol
- perindopril + bisoprolol

Renal insufficiency: 8 cases
Results: increased INR pharmacokinetic interaction
Results

- Number of hospitalised patients: 4261
- INR higher 4 : 137 (3.22 %)
- Number of drug-drug interaction: 45
  (32.9 % of patients with high INR, 1.05 % of all hospitalised patients)
### Drugs taking part in the interaction

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>12</td>
</tr>
<tr>
<td>Fluorokinolons</td>
<td>11</td>
</tr>
<tr>
<td>PPI</td>
<td>4</td>
</tr>
<tr>
<td>Furosemid</td>
<td>3</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>3</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>3</td>
</tr>
<tr>
<td>Normodipine</td>
<td>2</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>2</td>
</tr>
<tr>
<td>Metronidazol</td>
<td>2</td>
</tr>
<tr>
<td>Fluconazol</td>
<td>1</td>
</tr>
<tr>
<td>Gentamycin</td>
<td>2</td>
</tr>
</tbody>
</table>
Ahmad S: Lovastatin-Warfarin Interaction (Arch Intern Med. 1990 Nov)
2 beteget említ, vérvizeses szövődmény. Fokozott figyelmet javasol.


**2742 ambuláns statin kezelt beteg. 190 beteg (6,9%) 198 interakció.**

12.1% for simvastatin, 10.0% for atorvastatin, 3.8% for fluvasatin and 0.3% for pravastatin.
CYP3A4 gátlás a leggyakoribb.


**82 éves nőbeteg, 2,5 év stabil INR után. atorvastatin-simvastain csere. Mechanizmusa CYP3A4 gátlás. Másik enziminhibitor (diltiazem) adása 8 feletti INR-t és fatális intracraniális vérzést okozott. A simvastatin veszélyeire figyelmeztetnek.**

gemfibrozil, simvastatin, atorvastatin elkezdése az INR-t szignifikánsan növeli. A pravastatin biztonságos.

**A 6 hónapnál tovább tartó (egyszerre kezdett) kombinációt biztonságosnak tartják.**
Side effects in the diagnosis

- Patient's number: 4261
- Side effects number: 137 + 31 = 168
- Drug-drug interaction number: 16 + 45 = 61
- Side effect, as diagnosis: 5
- 3% of confirmed side effects

Slightly higher, than the hospitalised patients 1/1000
„Primum nil nocere!”

Thank You for Your attention!