DRUG INTERACTIONS I

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Drug interactions (DIs) are changes in efficacy or toxicity of the drug(s) as a result of interaction when two or more drugs are taken together.

These interactions can be detrimental because of the increased toxicity of the drug used or the decrease in effectiveness.

However, there are useful drug interactions as well. For example, the combination of diuretics and beta blockers in treatment of hypertension.

There are also non-clinical implications in DIs. However, drugs that are important in their interactions should be used cautiously.

The most frequently encountered medications are drugs with narrow therapeutic and toxic doses. They should be controlled very carefully in combinations where liver enzymes can be inhibited or induced.

At the same time, there is an interaction between prescription drugs and herbal products or non-prescription drugs.

The effect and severity of DIs can vary greatly from patient to patient. Especially elderly patients and those taking more than one drug are susceptible to drug interactions.

Interactions occur when the most active drug is started to be taken or when the drug intake is terminated. However, the time course of interactions may vary, taking into account the half-life of the drug.

If the potential dangers outweigh the benefits, an alternative medication should be chosen. What can be done is to adjust the dose of drugs when the interacting drug is started or terminated. Patient monitoring may also be necessary.

Particularly important is to report suspicious interactions or known interactions in newly introduced drugs.

EPIDEMIOLOGY

The actual frequency of DIs is consistently lower than the frequency of potential drug interactions. This rate is higher in hospitalized patients than in outpatients.

Real drug interactions may cause hospitalisation, rehospitalisation, and emergency department admissions.

More than 20% of reported adverse reactions are associated with drug interactions. Most of these are cases that cause serious or even high frequency deaths.

RISK FACTORS IN REAL INTERACTIONS

- Polypharmacy,
- Age,
- Genetic differences (polymorphisms).

SERIOUSNESS AND SEVERITY of DIs

- **Death,**
- **Life is in danger,**
- **Hospitalisation,**
- **Damage: significant, permanent or temporary change, damage and deterioration in patient organism function / structure, physical activity or quality of life,**
- **Congenital anomaly,**
- **The need for intervention to prevent permanent impairment or damage.**

DIs MECHANISMS

DIs are classified into 3 main groups according to their mechanism:

1. Pharmacodynamic (PD) DIs,

2. Pharmacokinetic (PK) DIs,

3. Pharmaceutical interactions (incompatibilities).

1. Pharmacodynamics (PD) DI: **The effect of a drug on the site of action change by another drug. These interactions are classified into three subgroups:**

a) Direct effect in receptor function,

b) Interaction with biological or physiological control procedures,

c) Additive / opposed pharmacological action.

PD interactions may occur at the receptor, at various receptors and at non-specific domains of action.

Interactions at the receptor site: Many drugs exert their effects by interacting with specific receptors located on the cell membranes or within the cytoplasm or nucleus. Interaction occurs due to the combination of agonist or antagonistic drugs to bind to specific receptors.

However, these interactions are sometimes beneficial to the patient in some clinical situations.
For example: removal of side effects induced by opiates with naloxane.

Additive / synergistic interaction (effect): **If two drugs with similar effects are given together, the effects can be additive.**

Interacting drugs Pharmacological/Toxicological Effect

NSAIDs,

Eg: When using benzodiazepine, increased sedative effect on alcohol intake. A similar situation can be seen with opiate analgesics and first-generation antihistamines with sedative properties. As a result of the interaction, CNS depression including respiratory depression, loss of consciousness, coma or death may occur.

The use of fluoxetine (SSRI) and clomipramine (TSA with serotonergic activity) causes serotonin syndrome in some patients.

Examples of additive or synergistic drug interactions

Interacting drugs	Pharmacological/Toxicological Effect
NSAIDs, Warfarin, clopidogrel	Increased risk of bleeding
Angiotensin-converting enzyme İnhibitors and K+ sparing diuretics	Increased risk of hyperkalemia
Verapamil and ß-adrenergic antagonists	Bradycardia and asystole
Neuromuscular blockers and aminoglycosides	Increased neuromuscular blockage
Alcohol and benzodiazepins	Increased sedation
Pimozide and sotalol	Increased risk of QT interval prolongation
Clozapine and co-trimoxazole	Increased risk of bone marrow suppression

Antagonism: **Occurs if two drugs have opposite effects.**

For example: the use of salbutamol (beta-2 agonist-Asthma, COPD) and metoprolol (beta-2 antagonist-Hypertension), which are counter-effects on the same receptor (may reduce the benefits of both medications).

Ex 2: Oxybutin (urinary incontinence/anticholinergic) - donepezil (dementia/cholinesterase inhibitor): Decreased cholinesterase inhibition efficacy.

Example 3: Furosemide (diuretic) - digoxin (heart failure): toxic effects on the heart may occur (digoxin increases and furosemide decreases potassium levels in the blood).

Eg 4. Sildenafil - organic nitrates. Severe hypotension may be seen by strengthening the effect of organic nitrates.

2. Pharmacokinetic (PK) DIs: The interactions in this section consist of 4 subgroups according to their mechanisms and stages:

Absorption

Distribution

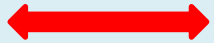
Metabolism

Elimination

a) ABSORBTION: **Insoluble complex formation by chemical bonding, changes in GI pH, changes in GI mobility, damage in GIS, induction or inhibition of drug carrier proteins, reduction of intestinal flora.**

Bond:

Some antibiotics:

Fluoroquinolones and tetracycline  **Fe, Ca, Calcium fortified foods, antacids.**

Outcome: Treatment failure (decreased absorption).

Phenytoin ⟷ antacids with Fe, Ca, Mg and continuous tube feeding.

Outcome: Loss of seizure control as a result of decrease in fenition serum level and failure of treatment.

SOLUTION: Fe, Ca or antacids should be taken 2 hours before or 2 hours after the drug to interact. The same recommendation applies to tube feeding.

Sucralfate (antiulcer) and cholestyramine (antilipemic) can be physically bond to certain drugs. These drugs are: chlorothiazide, phenytoin, ciprofloxacin, cyclosporine, digoxin, ketoconazole, valproic acid, fluoroquinolone and warfarin (inhibition of oral absorption).

SOLUTION: In some cases, it is necessary to use the drug 2 hours before the administration of sucralfate and cholestyramine. However, some combinations, such as warfarin-cholestyramine, should be avoided.

In general, interactions in the absorption stage may not cause a major clinical problem and can be addressed by adjusting the time of reception.

GI Motility

GI accelerates motility: erythromycin, metoclopramide.

GI slows down motility: opiates or anticholinergics.

Change in pH (esophagus: 5-7, stomach: 1-3, duodenum: 6.8)

In the acidic stomach, weak acids are more non-ionized, and therefore lipid soluble and readily absorbed. Weak bases are more ionized in the acidic stomach, limiting absorption. In the alkaline small intestine, drugs that are weak bases become more non-ionized, and therefore more lipid soluble and readily absorbed.

Absorption of itraconazole is impaired when gastric acidity is reduced. In patients also receiving acid neutralizing medicines (e.g. aluminium hydroxide) these should be administered at least 2 hours after the intake of itraconazole capsules.

b) DISTRIBUTION: substitution in protein binding site, induction or inhibition of drug carrier proteins.

The distribution of drugs depends on the total body water, the extracellular fluid, the percentage of adipose tissue and the capacity to bind to plasma proteins. Albumin and alpha-1 glycoprotein are the major plasma proteins to which the drugs bind. Some drug interactions occur due to competition rather than binding to these proteins. Clinically important interactions are seen that the drug is highly protein (more than 90%) binding and has a narrow therapeutic range. In addition, this type of interactions are more likely to occur in hypoalbuminemia, poor nutrition and liver diseases or chronic alcoholics.

For example: phenytoin-valproic acid intake. In this case, the free fraction of phenytoin increases due to the competition of the other drug instead of binding. In the normal case, the free fraction of phenytoin is usually 10-20% of the total serum concentration (10-20 µg / ml).

c) METABOLISM: hepatic uptake, induction or inhibition of drug carrier proteins, enzyme inhibition, enzyme induction.

Most drugs are metabolized in the liver by cytochrome P450 (CYP450) enzymes.

Enzyme induction: The induction of the enzyme by a drug may result in a decrease in the effectiveness of the other drug. It could take a few days or weeks. It is reversible. It may take 2-4 weeks for the enzyme to reach its normal value after interrupting the inducer reception.

Enzyme inhibition: Inhibition of the enzyme by a drug may result in the accumulation of other drugs and the appearance of toxic effects. After the first dose of inhibitor is seen and maximum inhibition occurs when the inhibitor reaches steady state level.

However, the overall results of this induction and inhibition are reversible for prodrugs.

CYP450 enzymes are a whole by their subfamilies, isoenzymes. The major CYP isoenzymes involved in the metabolism of drugs are CYP2D6, CYP2C9, CYP2C19, CYP3A4 / 5, CYP1A2.

Each isoenzyme acts as a major enzyme in the metabolism of a drug. However, more than one CYP450 enzyme may be involved in the metabolism of a drug.

Nortriptyline 100 mg / day

Therapeutic concentration: 50-150 ng / ml

Patient serum nortriptyline: 90 ng / ml

Paroxetine 40 mg / day

In the patient: Palpitations and dizziness

ECG: A slight sinus tachycardia

Patient serum nortriptyline: 359 ng / ml

Nortriptyline is metabolised by CYP2D6. Paroxetine is a drug that inhibits the enzyme CYP2D6. Therefore, with the addition of paroxetine to the patient as a result of inhibition of CYP2D6, nortriptyline level increased. Adverse effects in the patient are due to the high level of TSA as a result of nortriptyline-paroxetine interaction.

CYP3A4 / 5: The most common and important for interactions. Some drugs that are metabolized with this enzyme: atorvastatin, lovastatin, bubropion, imatinib, nifedipine, prednisone, sirolimus, ..

Inducers: glucocorticoids, rifampin, carbamazepine, phenobarbital, phenytoin leyic

Inhibitors: erythromycin, ketoconazole, itraconazole, clarithromycin, verapamil, grapefruit juice …….

Ex. Lovastatin-itraconazole combination: Itraconazole is an inhibitor of CYP3A4, thus the concentration of lovastatin plasma level significantly increase. As a result of this interaction, muscle damage may occur until rhabdomyolysis.

CYP2D6: It serves in the metabolism of 20-25% of drugs. Some drugs that are metabolized by this enzyme are tricyclic antidepressants, some SSRIs, beta blockers, codeine, clozapine, metoprolol, …….

Inductors: dexamethasone, rifampin.

Inhibitors: Bupropion, fluoxotin, paroxetine, duloxetine, cimetidine, quinidine, amiodarone, sertraline, terbinafine, sinacalset, …….

CYP2C9:

Some drugs that are metabolized by this enzyme: ibubrofen, phenytoin, warfarin ……..

Inductors: rifampin, rifabutin, carbamazepine ……

Inhibitors: Amiodarone, fluvoxamine, flucanozol ……

CYP2C19:

Some drugs that are metabolized by this enzyme: benzodiazepines, citalopram, TSAs, omeprazole, lansoprazole, ……

Inducers: rifampin, carbamazepine, prednisone ...

Inhibitors: lansoprazole, esomeprazole, fluvoxamine, fluoxetine, ticlopidine ……..

CYP21A2: **Approximately 15% of drugs are metabolized by this enzyme.**

Some drugs that are metabolized by this enzyme: caffeine, theophylline, TSAs ……

Inducers: **carbamazepine, phenobarbital, rifampin, insulin, cigarette smoke**

Inhibitors: **Fluvoxamine, cimetidine, ciprofloxacin, ……**

The web resource for the most comprehensive and up-to-date information on substrates, inhibitors and inhibitors of CYP450 enzymes:

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

d) ELIMINATION: **Hepatic secretion to bile, induction or inhibition of drug carrier proteins, urinary pH changes, active tubular secretion, tubular reabsorption, glomerular filtration rate.**

Urinary pH increase: citrate salts, furosemide, sodium bicarbonate, sodium lactate.

Those who lower urine pH: ascorbic acid, lithium, topiramate (anticonvulsant).

For example: Methotrexate-NSAI use may lead to an increase in the level of methotrexate and an increased risk of toxicity.