PRECLINICAL-CLINICAL STUDIES ON THE
PHARMACOLOGICAL INTERACTIONS
BETWEEN ANTIDEPRESSANTS AND
ANTIHYPERTENSIVES

- SUMMARY -

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Key words

Antidepressants, antihypertensives, pharmacokinetic interactions, pharmacodynamic interactions, depression, hypertension, blood pressure
I. GENERAL-THEORETICAL PART.
STUDY OF CURRENT KNOWLEDGE.

1. INTERACTIONS BETWEEN DRUGS

All effective drugs have the potential for producing both benefits and risks associated with desired and undesired effects. The particular response to a drug by a patient is driven in one way or another by the concentration of that drug, and sometimes its metabolites, at the effect sites within the body.

There can be drug-drug interactions in all pharmacokinetic processes: absorption, metabolism, distribution and excretion.

Metabolic drug interactions between drugs represent a major concern clinically for health care professionals and their patients. It has been estimated that some of the clinically significant drug-drug interactions may be the causes of adverse drug reactions (ADR) or causes of death. Cytochrome P450 (P450) binding is now widely recognized as a major focus for drug-drug interactions in the pharmaceutical industry. P450 metabolism-based drug-drug interactions, in vitro and in vivo, are now routinely part of the product labeling and advertising copy, often in incomprehensible detail.

2. PHARMACOKINETIC, PHARMACODYNAMIC INTERACTIONS BETWEEN ANTIDEPRESSANTS AND ANTIHYPERTENSIVES

<table>
<thead>
<tr>
<th>ANTIDEPRESSANTS</th>
<th>ANTIHYPERTENSIVE</th>
<th>ADVERSE DRUG REACTIONS</th>
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</thead>
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<tr>
<td>amitriptyline, clomipramine, desipramine, imipramine, fluoxetine, fluvoxamine, paroxetine, duloxetine</td>
<td>Propranolol</td>
<td>Increases concentration of propranolol (substrat of CYP1A2,2C19,2D6 )</td>
</tr>
<tr>
<td>amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptiline, fluoxetine, fluvoxamine, paroxetine, duloxetine</td>
<td>Propranolol</td>
<td>Increases concentration of antidepressants (propranolol is inhibitor of CYP2D6)</td>
</tr>
<tr>
<td>Amitriptyline, clomipramine, desipramine, imipramine, fluoxetine, paroxetine, duloxetine</td>
<td>Metoprolol</td>
<td>Increases concentration of metoprolol (substrat of CYP2D6)</td>
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<tr>
<td>Fluvoxamine, duloxetine</td>
<td>Bisoprolol</td>
<td>Increases concentration of bisoprolol (substrat of CYP3A4)</td>
</tr>
<tr>
<td>clomipramine, doxepin, citalopram, escitalopram, sertraline, mirtazapin, nefazodone, trazodone, fluvoxamine</td>
<td>Verapamil, diltiazem</td>
<td>Calcium channel blockers are inhibitors of CYP3A4, so they increases concentration of antidepressants</td>
</tr>
<tr>
<td>Antidepresive triciclics</td>
<td>Guanetidina</td>
<td>ADT scad efectul antihipertensiv</td>
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<tr>
<td>Tricyclic antidepressants</td>
<td>Clonidin</td>
<td>AD decrease antihypertensive effect</td>
</tr>
<tr>
<td>Trazodon, nefazodone</td>
<td>Prazosin, doxazosin</td>
<td>Increases hipotensiv effect (the antidepressants block alpha1 receptors and the antihypertensives are antagonists of this receptors)</td>
</tr>
<tr>
<td>Bupropion, venlafaxin, duloxetine</td>
<td>Antihypertensive</td>
<td>Antihipotensor effect is decreased by action of noradrenaline reuptake inhibition by antidepressants</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Clonidin</td>
<td>The antidepressant (central α2agonist) decreases the effectiveness of antihypertensiv (central α2 agonist)</td>
</tr>
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II. EXPERIMENTAL PART. PERSONAL RESEARCH ON CONTRIBUTIONS TO THE STUDY OF INTERACTIONS BETWEEN ANTIDEPRESSANTS AND ANTIHYPERTENSIVES

A. PRECLINICAL RESEARCHES

1. RESEARCH ON CHANGE OF HEART PARAMETERS ON MECANOGRAM OF A FROG JOINT VENTURE IN THE CASE OF ASSOCIATION AN ANTIDEPRESSANT AND A ANTIHYPERTENSIVE

I assigned a unique concentration of antidepressant with increasing doses of antihypertensive. Thus were associated: amitriptyline 25 mg/ml with atenolol/diltiazem and paroxetine 10 mg/ml with atenolol/diltiazem. The results were statistically and graphically.

The experiment found some pharmacodynamic interactions:

- Amitriptyline antagonizes the negativ inotrop and cronotrop effects of low concentrations of atenolol. Paroxetine antagonizes the negativ inotropic effect of atenolol, but potentiates the negative cronotrop effect

- The cardiotoxicity increases at the association antidepressant-calcium blocker with heart stopping at concentrations 100 times lower of diltiazem in combination with amitriptyline and 10 times lower in association with paroxetine. The negative cronotrop effect is increasing in combination with amitriptyline and the negativ cronotrop and inotrop effects of diltiazem is increasing in association with paroxetine.
2. RESEARCH ON EFFECTS ON RAT’S EKG IN THE CASE OF ASSOCIATION AN ANTIDEPRESSANT AND A ANTIHYPERTENSIVE

We studied the action of two antidepressants (amitriptyline and doxepin) on heart “in situ” on EKG of the rat. In this experiment we compared the preclinical effects achieved with a combination of calcium action blocker (verapamil).

In rats, the combination of verapamil - amitriptyline accelerates the depressant effects of antidepressant on AV conduction with AV block and atrial fibrillation. There was animal death. Combination verapamil - doxepin demonstrates an increase in depressant effects on AV conduction and atrial fibrillation production.

The combination of tricyclic antidepressants with calcium blocker from the group of phenilalkilamines type verapamil is contraindicated in terms of increased adverse cardiac effects by linking the two types of antidepressants and antihypertensives drugs.

3. RESEARCH ON INTERACTIONS BETWEEN ANTIDEPRESSANTS AND ANTIHYPERTENSIVES WITH PORSOLT TEST

The behavioural despair test (also called the Porsolt test or forced swimming test) is a test used to measure the effect of antidepressant drugs on the behaviour of laboratory animals (typically rats or mice).

The Porsolt test, test evasion (JRBoissier) and measurement of spontaneous motor activity examine the influence of antihypertensives (propranolol and metoprolol) on antidepressant action of amitriptyline in animals.

Definitely improve antidepressant action is observed in combination of amitriptyline and propranolol. It can be concluded that the combination of antidepressant action antidepressant with antihypertensive propranolol is better than treatment with antidepressant use only (ANOVA one-way test, Dunnett test). For the second antihypertensive – metoprolol – the antidepressant action is not better.

The results can be explained in two ways:
1) due to pharmacokinetic interactions due to metabolism of both substances
2) due to common mode of action to suppress the hypothalamic-pituitary-adrenal axis
B. CLINICAL RESEARCHES

4. CLINICAL STUDY ON PRIVIND FREQUENCY ASSOCIATION DEPRESSION-HYPERTENSION IN A LOT OF PATIENTS WITH DEPRESSION REGISTERED IN THE LABORATORY OF MENTAL HEALTH FOR A PERIOD OF 1 YEAR

We created a database that included data from the history (age, sex, risk factors, co-morbidity),

In our study, 94.6% of our patients who were diagnosed with depression and hypertension were treated with an antidepressant. Most of the prescribed antidepressants (62.5%) are antidepressants that, theoretically, increase the blood pressure lowering the effect of used antihypertensive. The next used (23.2%) are SSRI, 10.9% are represented by atypical antidepressants and 3.4% are represented by tricyclic antidepressants.

We performed the statistical analysis using From a logistic regression of depression on hypertension, age and sex: p=0.01352 (significant at 5% level) so patients with hypertension were not more likely to develop diagnosed depression when they don’t suffer of hypertension.

An interesting result was found about patients with chronic obstructive pulmonary disease, that make a difference between the lot of patients with depression, without hypertension ant the lot of patients with depression and hypertension (p=0.0035<0.05). An explication can be done by the pulmonary toxicity from the association antidepressants-antihypertensives.

5. CLINICAL STUDY ON ASUPRA ATERIAL PRESSURE CHANGES IN DEPRESSION DURING TREATMENT IN ASSOCIATION ANTIDEPRESSANTS AND ANTIHYPERTENSIVES

This clinical study wants to demonstrate that depression doesn’t increase blood pressure, but antidepressants do. By monitoring blood pressure in the case of tricyclic antidepressants and IRSA increases were seen in blood pressure.
It is well known that the rate of adverse drug reactions increases exponentially after a patient has been on multiple medications. Therefore it is very important to make efforts to reduce poliparmacy. However the number of medications cannot always be reduced without doing harm. This is why the understanding of the basis for drug interactions is so important.

Clinicians should be aware of the potential interactions and become familiar with the substrates, inhibitors, and inducers of the common enzymatic pathways responsible for drug metabolism. By understanding the unique functions and characteristics of CYP enzymes, physicians will be able to anticipate and manage drug interactions. This will enhance the use of rational drug therapy and better drug combinations.

Depression is associated with low levels of systolic pressure and less hypertension, while the use of certain antidepressants is associated with elevated systolic and diastolic blood pressure and hypertension.

Comparison of study groups, it was observed that subjects treated with tricyclic antidepressants have higher systolic blood pressure values (p = 0.003 <0.05), and diastolic blood pressure values (p = 0.00031 <0.05) and subjects treated with antidepressants that inhibit noradrenaline and serotonin selective reuptake have statistically significantly higher values of diastolic blood pressure (p=0.00041<0.05).

Frequent polimedication and frequent visits to various doctors, pharmacist – and, in particular, “patient pharmacist” (the patient mast address the same pharmacy and the same pharmacist for it to know the history of medication) – is the last barrier against possible adverse drug interactions.
SELECTIVE REFERENCES


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