

Practical aspects of drug interactions in the pharmacotherapy in otolaryngology, or the seven cardinal sins of pharmacological treatment in otolaryngological practice

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ABSTRACT:

Summary Drug interactions are a growing problem in the practice of otolaryngology. The use of drugs in patients treated with polypharmacy generates the risk of adverse drug interactions which requires specialized knowledge and active prevention. The most common interactions encountered by ENT physicians are identified on the basis of the analysis of medical order sheets and discussed in the article.

KEYWORDS:

otolaryngology, pharmacotherapy, drug interactions

Modern pharmacotherapy is based on polytherapeutic approach. Polypharmacy should lead to improved efficiency while reducing the risk of adverse effects. In otolaryngological practice, one may frequently encounter drug combinations that result in adverse effects due to interactions between drugs that are administered at the same time. Few practical analyses of this important clinical problem are available.

This study presents an evidence-based analysis of combinations of drugs recommended for simultaneous use in patients. One should keep in mind that when applying pharmacotherapy, ENT specialists should become aware of the treatments the patient is undergoing due to their concomitant disorders. Notably, one should always remember that the recommended drugs should not enter any adverse interactions with the drugs the patient is already taking. On the other hand, drugs used in the treatment of ear, nose, throat and pharyngeal disorders should not induce mutual coincidences that might result in adverse reactions (1,2,3).

A total of 500 pharmacotherapy order sheets issued by ENT specialists in both outpatient and inpatient setting were subjected to the analysis in this study. The analysis focused on the

search for drug combinations that, due to the pharmacokinetic as well as pharmacodynamic profiles of drugs being used create a risk of interactions that might lead to reduced efficacy of treatment and increased risk of adverse effects. Such combinations were identified in as many as 275 out of 500 prescriptions, i.e. in 55% of cases. The identified combinations were used as the basis for our list of seven most common sins of pharmacological treatment in otolaryngological practice.

SIN 1- INTERACTIONS OF ANTIHISTAMINE DRUGS

From the practical standpoint, the most important interactions in the group of antihistamine drugs are the pharmacokinetic interactions that occur at the stage of metabolism mediated by cytochrome P450 isoenzymes. Therefore, when selecting an antihistamine preparation, it is very important to consider the criterion of non-cytochrome P450-mediated metabolism. The role of this criterion was acknowledged by expert bodies formulating recommendations for the treatment of patients with allergic rhinitis (AR)[ARIA

2010] and urticaria [EAACI 2013], in which the lack of cytochrome P450 (1CYP450) metabolism is listed as an important factor to be considered when selecting the appropriate medication.

When selecting the antihistamine drug, one should take into account the potential risk of adverse interactions between antihistaminics and other drugs that the patient is also taking. This risk increases when the antihistamine drug is metabolized by cytochrome P450 enzymes. In order to avoid drug interactions and their clinical consequences including the need for treatment adjustment, drugs that are not metabolized by CYP450 should be used. This was also underscored in the aforementioned recommendations. **One may even venture the claim that the risk of interactions in polytherapy is the most important criterion for the selection of an antihistamine drug.** Among chronic disorders, allergic diseases and bronchial asthma are the group that particularly increases the risk of polypragmasia (i.e. situation when patients receive more than several drugs at the same time). **As shown in the available pharmacoepidemiological studies, the risk of excessive polytherapy increases by a factor of 4.5 in subjects with allergic disorders.** In other studies, the risk of polytherapy was particularly high in the treatment of cardiovascular disorders, pain, and allergic diseases. The increased risk of polytherapy is particularly affected by the multi-specialty health care model. The larger the number of physicians treating the patient, the higher the risk of polypragmasia, most commonly associated with the lack in coordination of the prescribed drugs and, in particular, the lack of coordination of the pharmacological treatment at the family physician or pharmaceutical care level. Polypragmasia is also escalated by the *prescription cascade* that has been described in the literature since the late 1990s. The prescription cascade occurs when an adverse effect of the treatment is considered a sign of new disorder which is followed by introduction of another pharmaceutical product. This happens quite commonly in case of adverse effects being induced by antihistaminics. In many cases, insufficient knowledge of drug interactions was observed in health care professionals (2). Therefore, it is worthwhile to have a look at the differences in the induction of interactions with other concomitant drugs in patients receiving antihistamine preparations. In the ENT practice, drug interactions are encountered most commonly when loratadine, cetirizine, or levocetirizine are used.

Loratadine, most of which is subject to the first-pass metabolism, forms an active metabolite of decarboethoxyloratadine (DEL). Food ingestion delays the absorption of the drug. Adverse reactions may include dry mouth, alopecia, impaired liver function, allergic reactions, supraventricular arrhythmias and sedation, possibly more intense than in the case of desloratadine.

The drug is metabolized by means of CYP 3A4 and CYP 2D6, resulting in a real risk of pharmacokinetic interactions with CYP3A4 inhibitor drugs (azole antifungals, erythromycin, clarithromycin, grapefruit juice). These interactions may lead to increased risk of cardiac arrhythmias.

A risk of interactions with CYP2D6 inhibitor drugs also exists and is particularly important in patients who are slow CYP 2D6 metabolizers and account for 7–10% of the Caucasian population [1,8].

It should be kept in mind that a switch from loratadine to desloratadine may be considered in patients at high risk of interactions. In case of desloratadine, no interactions with other concomitant drugs were observed to date, with the risk of pharmacokinetic interactions being considered low. This is particularly important in patients subjected to polypharmacy.

Cetirizine is an active metabolite of hydroxyzine formed in an oxidation process. Cetirizine's penetration into the central nervous system (CNS) is lower than that of hydroxyzine; however, the sedative effect of the drug is significant as compared to the other 2nd generation antihistamine drugs. The drug is characterized by low affinity towards muscarinic receptors, resulting in anticholinergic symptoms being observed in some patients receiving cetirizine, particularly manifested as dry mouth. The drug undergoes rapid absorption from the gastrointestinal tract, reaching peak concentration after ca. 30 minutes. The clinical effect of the drug also becomes evident after ca. 30 minutes and lasts for up to 24 hours, while the half-life of the drug is ca. 7.5 hours. Cetirizine is 93% bound to blood proteins, with 70% of the drug being excreted by the kidneys in an unchanged form and excretion being delayed in renal insufficiency.

Theophylline slightly reduces the clearance of cetirizine. Caution should be exercised upon simultaneous use of inhibitors of CNS function. No clinically significant interactions were observed with erythromycin, pseudoephedrine, azithromycin, ketoconazole, cimetidine, diazepam, and glipizide. Ritonavir increases the exposure to cetirizine. No clinically significant interactions with alcohol were observed; however, alcoholic beverages should be avoided when taking cetirizine due to the risk of exacerbation of CNS-related adverse effects (1,8).

Levocetirizine (the (R) enantiomer of cetirizine) is characterized by its affinity towards the type 1 histamine receptor (H_1) being twice higher than that of cetirizine; therefore, a dose of 5 mg may be used thus reducing the incidence of adverse effects such as sedation or anticholinergic symptoms. Pharmacokinetic parameters of levocetirizine are similar to those of cetirizine. About 85% of levocetirizine is eliminated from kidneys while the rest of the dose is excreted with feces. Both cetirizine and levo-

cetirizine may enhance the depressant effects of other concomitant drugs (tranquilizers, hypnotics, sedative antidepressants, antipsychotics, opioid analgesics). Both drugs may impair the ability to drive or perform complex tasks. No interaction studies were carried out for levocetirizine; the available results relate to the racemic drug. Slight (16%) reduction in cetirizine clearance is observed upon concomitant use of theophyllin. Levocetirizine does not alter the biological availability and activity of theophyllin. Levocetirizine taken together with alcohol or other CNS inhibitors may alter the CNS function; however, racemic cetirizine was not observed to enhance the effects of alcohol.

One should keep in mind that antihistamine drugs should not be combined with fenspiride due to the significantly increased risk of adverse effects, particularly CNS-related effects. There is no evidence to support the claim that concomitant use of combined antihistaminic drugs is better than monotherapy while there is no doubt that the risk of adverse effects is increased in the former case.

Of the antihistaminic drugs, **bilastine** is characterized by the lowest risk of pharmacokinetic interactions.

SIN 2 - INTERACTIONS OF ANTIBACTERIAL DRUGS

Antibacterial drugs are among the most common medications being prescribed in ENT practice. The concentration of the drug as well as the duration of its being retained within the infected compartment must be at an appropriate level to ensure their antibacterial efficacy. The efficacy of antibacterial drugs may be changed upon concomitant use of other drugs or upon the antibacterial drugs being taken in an inappropriate relation to meals.

Interactions of beta-lactam antibiotics

Beta-lactam antibiotics may increase the risk of bleedings in patients receiving oral anticoagulants. This is particularly the case for penicillin. The concomitant use of aminopenicillins and allopurinol is associated with an increased risk of skin lesions (rash) that should not be considered a sign of hypersensitivity to beta-lactams.

The use of cephalosporine antibiotics, particularly those of the 3rd generation may result in increased nephrotoxicity of aminoglycosides and loop diuretics, which should be kept if concomitant use of these drugs is required (1,2).

Antacids should be avoided in patients receiving cefaclor, cefuroxime, and cefpodoxime due to the risk of reduced absorption of antibiotics from the gastrointestinal tract.

Drugs increasing gastric pH levels should be avoided upon oral intake of cefuroxime axetil as this might reduce the absorption of the antibiotic from the gastrointestinal tract. This interaction pertains to both H₂-blockers and proton pump inhibitors.

Beta-lactam antibiotics may reduce the efficacy of oral hormonal contraceptives. Additional, non-hormonal methods of contraception are recommended during the antibiotic treatment as well as for 7 days after the treatment.

Alcohol should be avoided during the treatment with cephalosporine antibiotics.

Aminoglycoside antibiotics

When using aminoglycosides, one should avoid concomitant use of other drugs that increase their nephrotoxicity, particularly loop diuretics and platinum derivatives. Urine acidification (vitamin C, cranberry) should also be avoided due to the possible reduction of the efficacy of the aminoglycoside.

Clindamycin

Clindamycin may reduce the efficacy of oral hormonal contraceptives. Alcohol beverages should be avoided when using clindamycin.

Interactions of macrolides and azalides

When using macrolides, particularly erythromycin, delevicin and clarithromycin, one must keep in mind the significant risk of interactions resulting to the effects of these drugs on cytochrome P450 isoenzymes. All the above macrolides are actively metabolized, mainly by isoenzyme CYP3A4. Table 1 lists the most important drugs metabolized by CYP3A4 or inhibiting CYP3A4 and interacting with the macrolides aforementioned macrolides.

Simultaneous administration of macrolides and CYP3A4 inhibitors increases the risk of adverse reactions to macrolides. A low risk of pharmacokinetic interactions is associated with the use of roxithromycin, spiramycin, and azithromycin.

In particular, clarithromycin is capable of extending the QT interval in ECG records. The risk is additionally increased when other drugs that may extend the QT interval are administered together with macrolides. This relates mainly to antiarrhythmic drugs, cisapride, antipsychotic drugs, in particular typical antipsychotics, and drugs that might induce hypokalemia (loop diuretics, systemic glucocorticosteroids, laxatives) (1,2).

Since recently, azithromycin has been known to be associated with increased risk of cardiac arrhythmias. Therefore, azithromycin should be used with caution in patients treated for cardiac rhythm disorders and patients receiving drugs of proarrhythmic potential.

Macrolides increase the bioavailability of digoxin from the gastrointestinal tract while antacids reduce the bioavailability of macrolides from the gastrointestinal tract. Simultaneous use of clarithromycin with calcium antagonists of the 1,4-dihydropyridine group (amlodipine, felodipine, lercanidipine) should be avoided due to the high risk of acute non-inflammatory kidney failure

Interactions of fluoroquinolones with other concomitant medications

Upon simultaneous administration with theophylline, ciprofloxacin may increase the risk of adverse and toxic effects of theophylline. Ciprofloxacin increases the anticoagulant activity of warfarin. Concomitant use of fluoroquinolones with non-steroidal anti-inflammatory drugs (NSAIDs) leads to increased risk of seizures, particularly in elderly patients. Fluoroquinolones elongate the half-lives of diazepam and clonazepam. In such cases, the frequency of administration of both benzodiazepines should be reduced. Ciprofloxacin may increase the toxicity of methotrexate. Fluoroquinolones reduce the efficacy of oral hormonal contraceptives. On the other hand, norfloxacin enhances the anti-coagulant effect of coumarin derivatives and exerts antagonistic action against nitrofurantoin and furazolidone; thus, concomitant use of these drugs should be avoided. Antacids reduce the bioavailability of fluoroquinolones from the gastrointestinal tract (1,2).

Interactions of antibacterial medications with probiotics

Oral antibacterial drugs may reduce the efficacy of probiotic products. Probiotic that may be used with antibiotics include those that contain *Saccharomyces boulardii* as these microorganisms are insensitive to antibacterial activity of these drugs. When lactic acid bacteria preparations are used as probiotics, they should be administered not earlier than 2 hours after oral administration of the antibiotic; the interval may be longer when extended release formulations are used in the treatment.

Interactions with dietary supplements

Renal secretion of magnesium increases upon the use of aminoglycosides. On the other hand, when administering fluoroquinolones and tetracyclines, it is recommended to avoid simultaneous administration of supplements containing calcium,

Tab. I. Major CYP3A4-metabolized drugs and CYP3A4 inhibitors

DRUGS METABOLIZED BY CYP3A4	DRUGS INHIBITING THE ACTIVITY OF CYP3A4
Amitriptyline	Fluoxetine
Fluoxetine	Sertraline
Mirtazapine	Ketoconazole
Trazodone	Itraconazole
Haloperidol	Cisapride
Diazepam	Diltiazem
Alprazolam	Verapamil
Zaleplon	Valproic acid
Zolpidem	Grapefruit juice
Fentanyl	
Tramadol	
Azithromycin	
Amiodarone	
Nifedipine	
Simvastatin and atorvastatin	
Loratadine	
Omeprazole and lansoprazole	
Ethinylestradiol	
Sildenafil	

Tab II. Interactions of antibacterial medications with food

ANTIBACTERIAL DRUG	ADMINISTRATION IN RELATION TO MEALS
Amoxicillin	May be used in fasting condition or after meals
Phenoxymethylpenicillin	Use 1 hour before or 2 hours after a meal
Cloxacillin	Use 1 hour before or 2 hours after a meal
Cefaclor	Immediate-release tablets should be taken in fasting condition while extended-release formulations should be taken with meals
Ceftibuten	Use 2 hours before or 1 hour after a meal
Cefuroxime axetil	Use with meals
Tetracyclines	Should be taken with meals due to their gastrointestinal tract-irritating properties. Calcium-rich foods should be avoided when using the drug
Azithromycin	Tablets may be taken with or without meals while capsules should be taken 1 hour before or 2 hours after a meal
Erythromycin	May be used in fasting condition as well as after meals
Clarithromycin	May be used with or without meals
Roxithromycin	Use before meals
Spiramycin	Use in fasting condition
Clindamycin	May be used with or without meals
Ciprofloxacin	Use with or after a meal; do not drink milk or yogurt as it reduces the absorption from the gastrointestinal tract
Levofloxacin	Do not take with calcium-containing meals
Moxifloxacin	May be used with or without meals
Cotrimoxazole	May be used with or without meals
Metronidazole	Use 1 hour before or 2 hours after a meal; avoid high-fat meals when taking the drug

magnesium, iron, and zinc due to the inhibition of the absorption of antibiotics from the gastrointestinal tract. In case of trimethoprim, administration of folic acid is recommended at the daily dose of 0.4-1 mg.

Interactions of antibacterial medications with food

Table 2 lists data regarding the administration of antibiotics in relation to meals.

SIN 3 - INTERACTIONS OF DRUGS USED IN THE TREATMENT OF VERTIGO, TINNITUS, AND CEREBRAL CIRCULATION DISORDERS

Drugs used in peripheral circulation disorders, particular vertigo and tinnitus, may cause clinically significant interactions due to their pharmacodynamic mechanism of action. One should keep in mind that nicergoline and vinpocetine are often listed in the rankings of adverse effects due to such interactions (2,4,5,6). What's more, a safety notice for nicergoline was posted to the website of the Polish Office for Registration of Medicinal Products, Medical Devices and Biocidal Products drawing the public attention to possible adverse effects, risk factors and adverse interactions that might reduce the safety of nicergoline use.

INTERACTIONS OF NICERGOLINE

Nicergoline may enhance the effects of antihypertensive, antiplatelet, and anticoagulation drugs thus markedly increasing the risk of bleedings as well as the effects of drugs affecting the uric acid metabolism (allopurinol). Interactions with drugs metabolized by CYP450 2D6 are possible, particularly with relation to metoprolol, propafenone, tricyclic antidepressants, tramadol and dextrometorphan. Nicergoline may enhance the effects of these drugs. Consumption of alcohol while receiving nicergoline may enhance the drug's adverse effects on the CNS. When used with calcium antagonists such as amlodipine, nitrendipine, felodipine, or lercanidipine, nicergoline significantly increases the risk of hypotonia possibly increasing the risk of falls in elderly patients.

INTERACTIONS OF VINPOCETINE

Vinpocetine enhances the hypotensive effects of $\alpha 1$ adrenolytics, α -methyl dopa and vasodilators. Caution should be exercised when administering vinpocetine together with calcium antagonists. Synergy with other vasodilators is responsible for increased risk of steal syndromes, vertigo and falls, particu-

larly in geriatric patients. Caution should be exercised upon concomitant use with CNS-affecting drugs (benzodiazepines, hydroxyzine, phenothiazine neuroleptics, sedative antidepressants), anti-arrhythmic drugs, antihypertensive drugs and anticoagulants. Drugs that increase gastric pH levels may reduce the absorption of vinpocetine (6,7).

INTERACTIONS OF BETAHISTINE

Since betahistine is an analog of histamine, there is a possibility of interactions with other antihistamine drugs and therefore no combinations of both types of drugs are recommended. This pertains mainly to antihistamine drugs capable of significant permeation through the blood/brain barrier. Thiethylperazine (Torecan) also has a strong central antihistamine effect that should be taken into account in patients with vertigo. MAO inhibitors (including selective MAO-B inhibitors such as selegiline) may inhibit the metabolism of betahistine.

Interactions of medicinal products and dietary supplements including Ginkgo biloba extracts

Products containing ginkgo biloba extracts should not be taken by patients treated with antiplatelet agents (acetylsalicylic acid, thienopyridine derivatives, ticagrelor, cilostazol), oral anticoagulants (acenocoumarol, warfarin, rivaroxaban, dabigatran, apixaban), or heparin. In practice, an increased number of bleeding complications resulting from these interactions, including bleeding into the CNS, are observed. Concomitant use of NSAIDs and ginkgo biloba increases the risk of bleedings within the upper as well as the lower gastrointestinal tract. One should keep in mind that ginkgo biloba products may accelerate the metabolism of omeprazole and esomeprazole mainly via the CYP2C19 induction mechanism; as a consequence, the clinical efficacy of these drugs is reduced. When used with calcium channel blockers (amlodipine, felodipine, diltiazem), ginkgo biloba leads to increased risk of hypotonia, particularly in elderly patients. Isolated case reports of coma occurring after concomitant use of trazodone and priapism occurring in patients receiving risperidone are also available in the literature. Ginkgo biloba reduces the available levels and the efficacy of valproates. Ginkgo biloba may reduce the anxiolytic and hypnotic effects of benzodiazepines. It may also reduce the hypotensive effects of thiazide and thiazide-like diuretics.

Ginkgo biloba is a P-gp inhibitor and therefore should not be used with drugs such as dabigatran and rivaroxaban. Other drugs that may be involved in adverse interactions with ginkgo biloba products at the P-gp level are listed in Table 3.

Tab. III. P-gp substrate drugs involved in interactions with ginkgo biloba extracts

amitriptyline
ciprofloxacin
ciclosporine
digoxin
docetaxel
doxorubicin
L-DOPA
losartan
ondansetron
teniposide
vincristine
vinblastine

SIN 4 - INTERACTIONS OF SYSTEMIC GLYCOCORTICOSTEROIDS

Interactions of hydrocortisone

Hydrocortisone attenuates the effects of anticoagulants and antidiabetics. It enhances potassium loss, particularly when used in combination with loop diuretics. Simultaneous use of hydrocortisone and NSAIDs leads to increased risk of bleeding within the upper gastrointestinal tract. Phenobarbital, phenytoin, rifampicin, ephedrine and, to a lesser extent, pseudoephedrine impair hydrocortisone efficacy.

Interactions of prednisone

In case of simultaneous use of prednisone and phenobarbital, phenytoin, rifampicin, ephedrine and pseudoephedrine, the pharmacological activity of the drug may be reduced. On the other hand, enhancement of drug effects are observed upon combined use with estrogens and biphasic oral contraceptives. Concomitant use with diuretics (mainly loop diuretics) increases the potassium loss which is of particular importance in patients receiving cardiac glycosides due to the increased risk of cardiac arrhythmias. Prednisone inhibits the efficacy of oral anticoagulants, mainly acenocoumarol and warfarin; therefore, dosage adjustments are required in patients receiving these drugs. Prednisone may enhance the adverse effects of NSAIDs, mainly within the upper gastrointestinal tract.

Interactions of methylprednisolone

Methylprednisolone may be used in combination with anti-tuberculosis chemotherapeutics and, in the treatment of cancer, with alkylators, antimetabolites and vinca alkaloids. Simultaneous use of methylprednisolone and cyclosporine results in mutual inhibition of the metabolism of both drugs;

this, in turn, increases the likelihood of seizures. Similar as in the case of prednisone, caution should be used upon concomitant administration of NSAIDs due to the increased risk of upper gastrointestinal tract damage. Glycocorticosteroids may increase the renal clearance of salicylates. Caution should be exercised unconditionally upon simultaneous administration of acetylsalicylic acid and glyocorticosteroids to patients with hypothermia. CYP3A4 inhibitors (macrolides - erythromycin, clarithromycin, azole antifungals such as itraconazole) as well as 1,4-dihydropyridine derivatives of the group of calcium channel inhibitors may reduce the metabolism of corticosteroids and therefore appropriate dose reductions should follow. Hepatic enzyme inducers such as phenobarbital, phenylbutazone, phenytoin and carbamazepine may enhance the metabolism and reduce the clinical efficacy of methylprednisolone. As mentioned before, GCSs may reduce the reactions to anticoagulants, and therefore the coagulation parameters should be monitored. GCSs increase the demand for insulin and oral antidiabetics. The use of methylprednisolone along with thiazide diuretics increases the risk of hypokalemia and glucose intolerance. In individuals treated with corticosteroids at immunosuppressive doses, live attenuated viral vaccines should be avoided; inactivated vaccines or genetically engineered vaccines may be used, albeit the response to these vaccines may either be reduced or null. Simultaneous use of methylprednisolone with fluoroquinolones increases the risk of tendinitis and Achilles tendon rupture. Simultaneous administration of cholinesterase inhibitors (e.g. neostigmine, pyridostigmine) may induce myasthenic crisis. Through its mineralocorticoid activity, methylprednisolone may increase the arterial blood pressure and reduce the effects of hypotensive drugs. By increasing potassium secretion, methylprednisolone may enhance the activity of cardiac glycosides. Methotrexate influences the effects of methylprednisolone by its synergistic effect on the course of the disease, enabling possible steroid dose reduction. Methylprednisolone may partially inhibit neuromuscular blocks caused by muscle relaxants such as pancuronium. It may also enhance the reaction to sympathomimetic drugs such as salbutamol, or phenoterol, thus increasing their efficacy. Interactions with anxiolytic or antipsychotic drugs are also possible; in most cases, these are pharmacokinetic interactions requiring individual assessments.

Interactions of dexamethasone

Dexamethasone attenuates the activity of the antivitamin K group of anticoagulants and hypoglycemic agents. It also enhances the toxicity of cardiac glycosides, particularly in combination with diuretics due to the increased potassium loss. Concomitant ad-

ministration of NSAIDs leads to increased risk of gastrointestinal bleeding; however, in case of dexamethasone this risk is the lowest of those for all GCSs due to the fact of the lack of mineralocorticoid activity of dexamethasone. Phenobarbital, antiepileptic drugs, antihistamine drugs, rifampicin, ephedrine, and, to a lesser extent, pseudoephedrine, attenuate the effects of dexamethasone. On the other hand, the effects of dexamethasone are enhanced by estrogens.

SIN 5 - INTERACTIONS OF MUCOLYTIC, MUCOKINETIC AND ANTI-COUGH MEDICATIONS IN OTOLARYNGOLOGICAL PRACTICE

When applying expectorants (guaifenesin, sulfoguaiacol, bromhexine), mucokinetics (ambroxol) and mucolytics (erdosteine, acetylcysteine, carbocysteine), one should keep in mind that their efficacy is reduced by cholinolytic agents, including 1st-generation antihistamine agents. In case of oral acetyl cysteine and beta-lactam antibiotics, at least a 2-hour interval should be observed. No adverse interactions of anti-cough agents are observed for butamirate and levodropropizine. When using codeine and dextromethorphan, one should assess the potential pharmacokinetic interactions at level of cytochrome P450 isoenzyme 2D6 that is involved in the metabolism of these drugs. Expectorants, mucolytics and mucokinetic agents should not be used simultaneously with anti-cough agents, particularly with codeine and dextromethorphan as this might adversely modify the structure of bronchial secretion and increase the risk of complications. Codeine is absolutely contraindicated in patients below completion of 12 years of age (8).

SIN 6 - THE USE OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS IN COMBINATIONS WITH OTHER DRUGS CHARACTERIZED BY HIGH RISK OF ADVERSE INTERACTIONS

NSAIDs are one of the most common groups of drugs. They exert analgesic, anti-inflammatory and antipyretic effects which provides the grounds for their use in otolaryngological practice. It is worth remembering that NSAIDs may be involved in adverse interactions with many groups of medications affecting both the efficacy and safety of pharmacotherapy (2,3).

Most common interactions of NSAIDs include those with:

- diuretics (particularly loop diuretics) – attenuation of the diuretic effect, increased risk of nephrotoxicity
- beta-adrenolytics – NSAIDs reduce the efficacy of beta-blockers by inhibiting the release of renin. Beta-blockers, particularly beta-1 selective blockers enhance their efficacy by stimulating prostacyclin synthesis in

patients with arterial hypertension and heart failure (the effect being inhibited by NSAIDs)

- clonidines – NSAIDs reduce the efficacy of drugs of this group by increasing the total peripheral resistance.
- alpha-1 adrenergic receptor antagonists – NSAIDs may reduce the efficacy of these drugs as they induce the release of PGE₂ and PGI₂ that may be partially responsible for vasodilation.
- Angiotensin convertase inhibitors – NSAIDs inhibits bradykinin-induced release of prostaglandins; however, NSAIDs may increase the plasma levels of ACEIs by displacing ACEIs from their protein complexes. NSAIDs reduce the hypotensive and protective effects of this group of drugs on the cardiovascular system. At the same time, combinations of ACEIs and NSAID increase the risk of renal injury.
- AT1 receptor antagonists (sartans) – NSAIDs reduce the hypotensive effects of these drugs; combinations increase the risk of renal injuries.
- spironolactone – Simultaneous use of NSAIDs and spironolactone leads to a 7-fold increase in the risk of gastrointestinal bleeding (1,2)
- plant-based drugs and dietary supplements containing ginkgo biloba, ginseng, garlic and saw palmetto extracts – interactions between these plant extracts and NSAIDs increase the risk of bleedings
- standardized tomato extract (ZAAX) – due to its antiplatelet effects, concomitant use of this plant extract and NSAIDs increases the risk of bleedings
- drugs and supplements containing omega-3 acids – interactions with NSAIDs increase the risk of bleedings
- antiplatelet drugs – acetylsalicylic acid, clopidogrel, prasugrel, ticagrelor. Combinations with NSAIDs increase the risk of bleedings. It should be mentioned that dexketoprofen and ketoprofen are not involved in adverse interactions with acetylsalicylic acid used in anti-platelet doses.
- anticoagulants – antivitamins K (acenocoumarol, warfarin), dabigatran, rivaroxaban, apixaban. Combinations with NSAIDs increase the risk of bleedings. More frequent monitoring of INR is recommended in case of acenocoumarol and warfarin. In case of dabigatran (2 x 110 mg), rivaroxaban (1 x 15 mg), apixaban (2 x 2.5 mg) it is recommended to reduce the dosage to the respective values in parentheses.

SIN 7- THE USE OF DIETARY SUPPLEMENTS INSTEAD OF MEDICINAL PRODUCTS

Recent years witnessed a hyperdynamic increase in the consumption of dietary supplements. Unfortunately, along with

the increased consumption, the risk of potential adverse effects and interactions being induced by these products also increases. What's more, practice shows that both patients and, what's worse, physicians, are not completely aware of which products available at the market are medicinal products and which are the dietary supplements.

Currently no good definition of a dietary supplement is available. Researchers accept dietary supplements as the concentrated source of nutrients and other constituents with physiological activities. No pharmacokinetic parameters, such as bioavailability of the pharmacokinetic profile, are determined in case of dietary supplements; in medicinal products, these parameters are crucial for determination of dosage and administration frequencies. In case of supplements, the lack of pharmacokinetic data leads to the lack of toxicodynamic profile which is indirectly associated with the consequences of adverse interactions between supplements as well as between supplements and concomitant medications not being taken into account. As mutual interactions between medicinal products and dietary supplements may be

hazardous, it is recommended to avoid dietary supplements if they are not required; when planning to take dietary supplements while simultaneously receiving medications, one should on all occasions verify whether no hazardous interactions may occur between the products. In case of plant extract-based supplements, possible adverse interactions with concomitant drugs must always be taken into account.

Finally, one other issue deserves our attention. Pharmacies often replace the medicinal products prescribed by the physicians with other products, sometimes even with dietary supplements. Although it is legally acceptable to replace a reimbursed drug by its cheaper equivalent, it is illegal to replace medicinal products with dietary supplements.

As seen from the aforementioned facts, the choice of drug to be used in clinical practice must not be made at random. When making a choice, one should take into account not only the efficacy of treatment, but also the potential risks associated with adverse effects and interactions with other drugs (8).

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