PHEI «Kharkiv international medical university»
Department of fundamental general scientific disciplines

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DRUG-FOOD INTERACTIONS: BENEFIT OR HARM

Reporter: Saivamshi Thota, student of the 3-rd course
KhIMU

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INTRODUCTION

Today, the quality of medical care is vital. Ingestion of food in general or certain food products at the same time with some drugs may affect the bioavailability, pharmacokinetics, pharmacodynamics and therapeutic efficacy due to changes in the drugs absorption and metabolism. The practical physician has to take into account that dietary factors can influence the drug`s pharmacokinetics and pharmacodynamics.

Food products can interact with drugs and increase the risk of adverse reactions. The lack of a positive effect of the therapy in patients may be due to the food-drug interaction of the drugs.

According to the Food and Drug Administration (FDA), there are at least 200 drugs whose efficacy or toxicity is affected by food. The oral route of administration is one of the most common ways of drugs administering to the body, so the most important factor to improve the treatment effectiveness in the case of oral administration of a drug is their rational combination with food.[8]

The aim of our scientific research is to conduct an analytical review of scientific literature data on the effect of food products and their components on the pharmacological activity of the drugs.

CLINICALLY SIGNIFICANT CASES OF INTERACTION BETWEEN DRUGS AND FOOD.

We want to start our analyses with cross-sectional, descriptive study Abdollahi M and co-authors [1].

This study was conducted on 400 inpatients admitted to the Department of Internal Medicine of a teaching hospital in Mashhad, Northeast Iran, within 20 March 2013 to 20 April 2013. The potential food-drug interactions were evaluated for 19 commonly prescribed medications. The main factors (e.g., age, gender, education level, number of medications, and duration of the disease) that may place the patients at risk of potential food-drug interactions were analyzed for each patient.

Results: Out of the 400 patients, 44.5% of them were male. The median age of the patients was 47 years. Most of the hospitalized patients were suffering from cardiovascular and gastrointestinal diseases. Furthermore, 89.8% of the patients (n=359) often consumed their medicines at an inappropriate time with respect to meals. The prevalence rates of potential food-drug interactions regarding the 19 investigated drugs in the study participants are briefly summarized in Table 1.

Table 1. Potential interactions between foods/nutrients and drugs prescribed for inpatients

Drugs	Food/nutrients	Mechanism/effect	Recommendation	Number of cases with potential interaction/ all cases (%)
Carvedilol	Foods in general	Administered with foods, decreases orthostatic hypertension	To be administered with foods	21/42 (50%)
Diclofenac	Foods in general	Decrease risk of lesion in the gastrointestinal tract	To be taken with foods to decrease the risk of gastric mucosa lesion	13/19 (68.4%)
Isosorbide dinitrate	Foods in general	Decrease absorption rate of drug	Better to be administered with empty stomach	125/178 (70.2%)
Magnesium Hydroxide	Protein	Decreases the neutralizing capacity of the antacid	To be avoided with foods rich in protein	0/298 (0%)
Spironolactone	Milk and meat (potassium)	Retains potassium (K)	To avoid administration with foods rich in K	35/56 (62.5%)
Ranitidin	Milk and meat (vitamin B12)	Depletes the absorption of vitamin B12	Not to eat foods rich in vitamin B12 close to or during the administration of the drug	58/96 (60.4%)

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Nitroglycerin	Foods in general	Decreases the absorption rate of drug	Better to be administered with empty stomach	77/77 (100%)
Triamterene-H	Cheese, fried egg, and meat	Increases the absorption of the drug and depletes sodium	To be administered with fatty foods To avoid administration with foods rich in Na	14/35 (40%)
Metronidazole	Foods in general	Administered with foods, it decreases stomach upset	To be taken with food	26/26 (100%)
Ferrous sulfate	Food in general Foods high in Vitamin C	Decrease absorption of the drug Increase absorption of the drug	To avoid administration with foods To administrate with Vitamin Crich food	62/74 (83.8%)
Metoprolol	Food in general	Increase absorption of the drug	To administer with foods	140/196 (71.4%)
Co-trimoxazole	Food in general	Administered with foods, increases stomach upset	To avoid administration with foods	22/30 (72.3%)

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Captopril	Foods in general	Decreases the absorption of the drug	To be consumed one hour before or two hours after meals	137/158 (86.7%)
Aspirin	Food/ beverage rich in vitamin C and vitamin K	Depletes the absorption of the vitamins	Not to eat foods rich in vitamins C and K, folic acid, thiamine, and amino acids, close to or during the administration of the medicines	0/298 (0%)
Omeprazole	Chicken and milk (vitamin B12)	Depletes the absorption of vitamin B12	No to eat foods rich in vitamin B12 close to or During the administration of the drug	34/122 (27.9%)
Amiodarone	Food in general Grapefruit juice (not available on hospital menu)	Increases the rate and extent of absorption Drinking grapefruit juice with this medication may increase the risk of dangerous side effects	To be administered in a consistent manner relative to food intake To avoid administration with grapefruit juice	14/21 (66.7%)
Clidinium – C	Foods in general	Reduces digestive secretions	To be administered 30-60 min before food	33/76 (43.4%)
Lovastatin	Evening meal Grapefruit juice (not available on hospital menu)	Increases the efficacy of drug Drinking grapefruit juice with this medication may increase the risk of liver damage	To be administered with evening meals To avoid administration with grapefruit juice	49/63 (77.8%)
Propranolol	Milk (proteins	Increases the bioavailability of the drug	To be administered with foods high in protein	28/42 (66.7%)

A cross-sectional epidemiological study was conducted, using household surveys. S. J. F. Neves and co-authors [2] studied the prevalence of potential interactions between drugs and food in a group of elderly and senile patients. The prevalence of potential drug-food interactions was 58.5%. While the maximum risks of developing side reactions due to such an interaction were present in patients who took several drugs at the same time with food.

The following groups of drugs with a high potential risk of interaction with food were most common among the prescriptions:

- **hypoglycemic drugs (6.8%),**
- **diuretics (13%),**
- **blockers of the renin-angiotensin-aldosterone system (11.2%),**
- **beta-blockers (2%)),**
- **analgesics (8.4%).**

Among drugs with high risks of developing potential adverse reactions due to interactions with food, **captopril (36.3%), propranolol (17.9%), metformin (15.1%), alendronate (6.5%) and furosemide (2.1%)** are leaders.

RISK FACTORS FOR DRUG-FOOD INTERACTIONS

These studies show that the following factors are statistically associated with a higher risk of potential food-drug interactions:

- **age**
- **simultaneous reception of a large number of drugs**
- **duration of the pathological condition/disease**
- **the presence of certain chronic diseases (diabetes mellitus)**

PHARMACOKINETIC TYPE OF DRUG AND FOOD INTERACTION

Food can change the absorption, metabolism, distribution and excretion of drugs.

FOOD EFFECT ON THE DRUGS ABSORPTION

Drug-food interaction involving plasma proteins. One of the main transport proteins is the Organic Anion Transporting Polypeptides (OATP) protein group. This family of transporter proteins is found in the liver and intestines. The main function is the transport of endogenous substrates (bile acids, thyroid hormones, prostaglandins, glucuronides, bilirubin), as well as the absorption of food and drugs.[3] Numerous human studies have proven a clinically significant reduction in intestinal absorption of statins, protease inhibitors, fexofenadine, midazolam, montelukast, aliskiren, and talinolol when taken orally along with grapefruit, orange, and apple juices. [4,5].

FOOD EFFECT ON THE DRUGS METABOLISM

Clinically significant interactions of drugs and food at the stage of metabolism are mediated through the induction or inhibition of enzymes of the cytochrome P450 system of the liver and P-glycoprotein. Many food products have the ability to influence the P450 enzyme system.

Vegetables and fruits are able to inhibit the activity of P450 enzymes:

- **tomatoes inhibit CYP1A1, CYP1B1,**
- **red pepper inhibit CYP1A2, CYP2A2, CYP3A1, CYP2C11, CYP2B1, CYP2B2, CYP2C6;**
- **grapefruit inhibit CYP3A4, CYP1A2, MRP2 and P-glycoprotein isoenzymes;**
- **mango inhibit CYP1A1, CYP1A2, CYP3A1, CYP2C6, CYP2E1,**
- **apple inhibit CYP1A1 isoenzyme.**

Foods can also act as enzyme inducers:

- **broccoli and Brussels sprouts activate the CYP1A2 enzyme;**
- **mandarine stimulates the activity of the CYP3A4 isoenzyme.[6]**

Induction / inhibition of metabolic enzymes affects the half-life of the drug:

1) if the half-life decreases (enzyme induction), then it is necessary to increase the dose of the drug or reduce the time interval between its doses;

2) if the half-life increases (enzyme inhibition), then it is necessary to reduce the dose of the drug or increase the intervals between its doses.

Examples of fruits and fruit juices drugs interaction

Drug	The nature of the interaction	Recommendation
Grapefruit juice		
Cyclosporine	Juice blocks the enzymes of the cytochrome P450 and IA2 system (CYP3A4 and CYP1A2) in the intestine; increased levels of cyclosporine in the blood; increased likelihood of side effects	Avoid sharing. Take drugs on an empty stomach / 1 hour before meals or 2 hours after.
Lovastatin	An increase in the bioavailability of lovastatin by 1400%, which can lead to the accumulation of drugs in the blood, and the possible development of side effects	Avoid sharing. Take drugs on an empty stomach / 1 hour before meals or 2 hours after.
Itraconazole	Elevated blood levels of itraconazole leading to harmful side effects	Avoid sharing. Take drugs on an empty stomach / 1 hour before meals or 2 hours after.
Nifedipine	An increase in the level of nifedipine in the blood; increased absorption of nifedipine	Use with caution, monitor the patient's condition. Apply drugs for 30 minutes. before meals. Dose adjustment is possible.
Carbamazepine	An increase in blood levels of carbamazepine, leading to the development of harmful side effects	Avoid sharing. Take drugs on an empty stomach / 1 hour before meals or 2 hours after.

Cranberry juice		
Warfarin	**Strengthening the effects of warfarin; the appearance of bleeding**	**Avoid sharing. Take drugs on an empty stomach / 1 hour before meals or 2 hours after.**
Diclofenac	**Suppression of the metabolism of diclofenac**	**Dose adjustment is possible.**
Orange juice		
Digoxin	**Decreased absorption of digoxin, which leads to a decrease in the concentration of drugs in the blood**	**Use with caution, monitor the patient's condition. Apply drugs for 30 minutes. before meals. Dose adjustment is possible.**
Atenolol	**Moderate decrease in the bioavailability of atenolol**	**Dose adjustment is possible.**

Pomegranate juice		
Tolbutamide	**Inhibition of the activity of the CYP2C9 isoenzyme; increased bioavailability of tolbutamide**	**Avoid sharing. Take drugs on an empty stomach / 1 hour before meals or 2 hours after**
Carbamazepine	**Possible effect on pharmacokinetics carbamazepine by inhibiting the activity of the CYP3A isoenzyme**	**Dose adjustment is possible**
Apple juice		
Fexofenadine	**Significant reduction in plasma bioavailability of fexofenadine**	**Use with caution, monitor the patient's condition. Apply drugs for 30 minutes. before meals. Possible dose adjustment**
Raspberry		
Midazolam	**Inhibition of CYP3A activity; suppression of the effects of midazolam**	**Use with caution, monitor the patient's condition. Apply drugs for 30 minutes. before meals. Possible dose adjustment**

CONCLUSIONS

Drugs and food products can interact with each other at the pharmacokinetic level. Simultaneous intake of food and drugs can change absorption and metabolism process, which will have a direct impact on the efficacy and safety profile of pharmacotherapy.

Ways to solve:

-Future studies are warranted to further evaluate the real outcomes of food-drug interactions. -Knowledge of the mechanisms of compatibility of drugs and individual food products, a rational combination of drugs and food will help reduce unwanted side effects and optimize ongoing drug therapy for patients.

-When prescribing drug therapy, the doctor must necessarily stipulate the patient's diet in order to reduce the risk of such interactions.

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Thanks for your attention