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Review article

PHARMACOKINETIC AND PHARMACODYNAMIC INTERACTIONS BETWEEN DRUGS AND FOOD

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Abstract

Drug interactions occur when the effect of one drug changes because of the drug interacting with another drug, beverages, herbs, and foods. This interaction can be pharmaceutical, pharmacokinetic (increasing or decreasing the bioavailability of drugs), and pharmacodynamic (synergistic and antagonistic). Given the fact that most patients who are regular users of drugs are geriatric patients, the physiological changes that occur in this age group regarding the pharmacokinetics and pharmacodynamics of drugs make it even more important to take care of giving drugs in effective doses, avoiding failure of therapy and overdose because of interactions that may occur. The most common and dangerous interactions are drug-drug interactions, but serious interactions have also been documented that could endanger patients' health even between medications with different foods. Therefore, there is a need for a higher awareness of medical staff in giving adequate advice to patients regarding drug interactions they use with certain foods.
Some of the foods that give interactions with different drugs, and that are of clinical importance are foods rich in tyramine, histidine, vitamin K, protein, fats, and fiber; milk and milk products; grapefruit, St. John's wort, and caffeine.

Keywords: interactions, drugs, foods, pharmacokinetic, pharmacodynamic

1. Introduction

For the maintenance of physiological processes, the body needs to be constantly nourished with all kinds of foods, which contain the necessary amounts of vitamins, minerals, proteins, fats, and sugars. But the situation changes when it comes to people who are under therapy, especially patients who are on chronic polytherapy. Numerous studies have confirmed the interaction between medication and food, raising the alarm that therapy may fail because of the interaction occurring. Drugs can interact with different mechanisms with certain foods. A drug interaction is a situation in which a substance affects the activity of a drug, i.e., the effects are increased or decreased, or they produce a new effect that neither produces on its own. These interactions may occur out of accidental misuse or due to a lack of knowledge about the active ingredients involved in the relevant substances (1).

Interactions between food and drugs may inadvertently reduce or increase the drug effect. Most clinically relevant food-drug interactions are caused by food-induced changes in the bioavailability of the drug. Since the bioavailability and clinical effects of most drugs are correlated, bioavailability is an important pharmacokinetic effect parameter. (1,2). On the other hand, drug efficacy, side effects, and toxicity often are highly dependent on drug metabolism determining the activation and/or elimination of the respective compound. In humans, cytochromes P450 are the most important drug-metabolizing enzymes of the first phase of drug biotransformation. Their activity can vary due to interindividual genetic differences, but it can be changed also by inhibition or induction of the enzymes by their substrates or other compounds. (3,4).

The gastrointestinal absorption of drugs may be affected by the concurrent use of certain foods or other

agents that, have a large surface area upon which the drug can be absorbed, bind or chelate, alter gastric pH, alter gastrointestinal motility, or affect transport proteins such as P-glycoprotein. A reduction only in the absorption rate of a drug is seldom clinically important, whereas a reduction in the extent of absorption will be clinically important if it results in subtherapeutic serum levels. (1,5).

Induction is a term used to describe a physiological adaptive response to continued xenobiotic exposure. It is characterized by enhanced gene transcription and/or translation, stabilized messenger ribonucleic acid, or inhibited protein turnover. The result can be increased amounts of proteins that determine drug disposition, such as metabolic enzymes or transporters. The dose of the inducer determines its cellular concentration and hence the extent of induction. The resulting clinical effects usually start within a few days of repeated administration. After the withdrawal of the inducer, reversal is generally complete within 1 week. (6).

Inhibition of hepatic enzymes is much more frequent than induction, starts faster, within 2-3 days, and is repaired faster. This interaction reduces the metabolism of the drug and thus increases its plasma concentration with the potential for toxicity. (7).

Pharmacodynamic interactions between drugs and food are fewer compared to pharmacokinetics. A synergistic effect has been observed between anticoagulants (warfarin) with foods rich in Omega 3 and vitamin E. On the other hand, foods rich in vitamin K antagonize the anticoagulant effect of warfarin. (7,10).

Dangerous interactions have been observed between antithyroid drugs and foods containing large amounts of iodine, while alcohol consumption by diabetic persons undergoing insulin therapy or oral preparations may result in severe hypoglycemia. Also, the use of alcohol during treatment with paracetamol can give hepatotoxicity (10).

2. Aim of the study

Given the fact that the effectiveness and toxicity of drugs can be affected by the presence of certain foods, the purpose of this study is:

- To review the scientific data related to the interaction of drugs with certain foods
- Evaluation of clinical significance and consequences that patients may have if drug-food interaction occurs
- Raising the awareness of the medical staff for giving advice to patients regarding this issue
- Educate patients about the proper use of therapy, adhering to the advice of doctors and pharmacists

3. Materials and methods

The literature survey was conducted by extracting data from different reviews and original articles on general or specific clinically consequential drug-food interactions. The review was systematically conducted by searching PubMed, Medline, Cochrane, Web of Knowledge, Scopus, and Google Scholar databases for original research, using relevant search terms and the combinations thereof, “the impact of food on the effect of drugs; drug and food interactions; pharmacokinetic interactions of drugs, pharmacodynamic interactions of drugs, the clinical significance of drug interactions. Inclusion was limited to publications available in the English language and was not limited by dates or place of publications. The full text of each included article was critically reviewed, and valuable information was summarized by data interpretation.

4. Results and discussion

From the literature used in this study, it turns out that there are many interactions between drugs and food. These interactions are encountered with almost all foods with certain medications. Fortunately, not all interactions significantly affect the effect of drugs, and as such are not of clinical significance, but on the other hand some interactions are quite serious putting at risk the failure of therapy and the lives of patients.

Physical and chemical interactions between drugs and excipients can affect the chemical nature, the stability and bioavailability of drug products, and consequently, their therapeutic efficacy and safety (8, 9). Most drug-food interactions are pharmacokinetic, greatly altering the bioavailability of drugs. Decreased or increased drug absorption has been observed with certain foods. Absorption of drugs may increase or decrease because of changes in the pH of the digestive system, gastric emptying, intestinal motility, damage to the bacterial flora, and the formation of indigestible complexes (7).

Drug interactions with certain foods may be nonspecific, and the presence of any food may reduce the absorption of certain drugs. Thus, taking oral penicillin (18), ACE- inhibitors (19), sartans (20), proton pump inhibitors (21), aspirin, paracetamol (22), penicillamine (23), alendronate and ibandronate (24) in the presence of any food results in decreased absorption of these drugs.

Different food contents interact specially with certain drugs. Mineral-rich foods such as: Fe, Ca, Mg, Al, Zn form insoluble complexes with these drugs: tetracyclines, quinolones, penicillamines, levodopa /carbidopa, and thus greatly inhibit their absorption (2,7).

On the other hand, fatty foods can increase the absorption of some drugs such as: antimycotics (albendazole, griseofulvin, ketoconazole, etc.) and calcium channel blockers (25, 1).

Phenytoin can be attacked by foods high in protein, which reduces absorption, while foods rich in sugars increase their absorption. Knowing that this drug has a narrow therapeutic range, patient monitoring is needed to avoid toxicity and safely control epileptic seizures. (26, 1).

Most interactions are observed with grapefruit and St. John's wort plant. Grapefruit increases the absorption of calcium channel blockers, digoxin, cyclosporine, tacrolimus, statins and erythromycin, while delaying the absorption of levothyroxine (27, 1, 7). St. John's wort plant has the opposite effect to grapefruit, so it reduces the absorption of digoxin, cyclosporine, tacrolimus and statins (28, 29, 1).

Table 1 summarizes the most important drug interactions with certain foods, which affect the absorption of drugs resulting in an increase or decrease in bioavailability.

From the table we can see that all types of foods with certain composition (minerals, proteins, fats, sugars) can interact with drugs or different groups of drugs, which can result in consequences on the disease and health of patients.

Table 1: Interactions between drugs and food that increase or decrease absorption

Drugs	Food	Drug-Food Interaction
Penicillamine Quinolones Tetracycline	Foods containing Al, Mg, Fe, Ca, Zn	Form poorly soluble complexes
Antimycotics (Albendazole, Griseofulvin, Ketoconazole, etc.)	Foods rich in fats	Increase absorption
Phenytoin	Carbohydrate-rich foods Protein rich foods	Increase absorption Decrease absorption
Levodopa/ Carbidopa	Foods containing Fe	Form poorly soluble complexes

Calcium channel blocker	Foods rich in fats Grapefruit juice	Increase absorption Increases the bioavailability
Digoxin	Grape fruit juice, Ginseng Hypericum perforatum Foods rich in fiber	Increase absorption Decrease absorption Delay absorption
Proton pump inhibitors	With food (any type)	Reduce bioavailability
Cyclosporine	Grape fruit juice/ food Hypericum perforatum	Increases bioavailability Reduce bioavailability
Tacrolimus	Grape fruit juice Hypericum perforatum	Increase absorption Decrease absorption
Statins	Grapefruit juice Hypericum perforatum	Increase absorption Decrease absorption
Penicillamine	With food (any type)	Decrease absorption
Mercaptopurine	Milk	Reduce bioavailability
Levothyroxine	Milk/dairy products Grapefruit juice	Decrease absorption Delay the absorption
Propanolol	Milk	Decrease absorption
Glimepiride	With food (any type)	Absolute bioavailability
Alendroat/ Ibandronate	All food and drinks	Decrease absorption
ACE-inhibitors	With food (any type)	Decrease absorption
Losartan/ Eprosartan Valsartan/ Telmisartan	With food (any type)	Increase absorption Decrease absorption
Aspirin/ Paracetamol	With food (any type)	Decrease absorption
Erythromycin	Grapefruit juice	Increases bioavailability
Oral Penicillins (amoxicillin, ampicillin, flucloxacillin, pivampicillin, etc)	With food (any type)	Decrease absorption

Also, different foods affect liver enzymes, namely Cytochrome P450 by inhibiting/stimulating these enzymes, thereby reducing/increasing the biotransformation of drugs. Reduction of biotransformation of drugs results in a higher concentration of the drug in the blood which can lead to toxicity, while induction of hepatic enzymes leads to faster biotransformation of the drug resulting in decreased concentration below therapeutic values failing therapy (6,7).

Interactions affecting drug metabolism are most seen in grapefruit and St. John's wort.

Grapefruit inhibits liver enzymes and thus can cause toxicity from the following drugs: carbamazepine, benzodiazepines, ivabradine, terfenadine, sertaline, and fluvoxamine (27, 7, 30).

Dangerous and high-cost interactions have been observed between cyclosporine (immunosuppressive) and St. John's wort. In some studies, conducted, the rejection of the transplant (heart and kidney) is observed because of the reduction of the therapeutic concentration of cyclosporine because of the use of this plant (11, 12, 13).

Table 2 summarizes the interactions between drugs and foods that result in an increase or decrease in drug biotransformation because of inhibition and induction of cytochrome P450.

Table 2 Drug interactions with food that interfere with drug metabolism

Drugs	Food	Drug-Food Interaction
Phenytoin/ phenobarbital	Foods rich in pyridoxine (B6)	Induction of hepatic enzymes
Carbamazepine	Foods rich in nicotinamide (B3)/ Grapefruit juice	Inhibition of hepatic enzymes
Terfenadine	Grapefruit juice	Inhibition of hepatic enzymes
Benzodiazepines	Grapefruit juice	Inhibition of hepatic enzymes
Indinavir	Hypericum perforatum	Induction of hepatic enzymes
Ivabradine	Grapefruit juice	Inhibition of hepatic enzymes
Oral contraceptives	Hypericum perforatum	Induction of hepatic enzymes
Sertraline/ Fluvoxamine	Grapefruit juice	Inhibition of hepatic enzymes
Theophylline	Foods rich in protein/ Hypericum perforatum	Inhibition of hepatic enzymes
Theophylline	Foods rich in sugars	Induction of hepatic enzymes
Cyclosporin	Hypericum perforatum	Induction of hepatic enzymes

Interactions between drugs and food can also affect the pharmacodynamics of drugs, resulting in synergism or antagonism of the effect of the drug, or the presentation of a new effect of this combination, which is often a toxic condition (1,10)

The anti-coagulant warfarin antagonizes vitamin K1 recycling leading to the depletion of active vitamin K1. However, green leafy vegetables or "greens" contain large amounts of vitamin K1 reversing its depletion. Similarly, renin-angiotensin system inhibitors increase plasma potassium [K+] levels due to a reduction in aldosterone activity. However, foods rich in [K+] such as oranges and bananas may cause hyperkalemia resulting in cardiac arrest and death due to myocardial arrhythmia. In addition, a hypertensive crisis can result from the ingestion of tyramine-rich foods (fermented foods such as wine and cheese) in conjunction with monoamine oxidase inhibitors (MAOIs). MAOIs used to treat depression, inhibit the breakdown of endogenous and dietary amines. Consequently, MAOIs reduce the breakdown of tyramine, a precursor of catecholamines, and raise catecholamine biosynthesis causing a hypertensive crisis (14,15).

The combination of isoniazid with histidine-rich foods results in so-called histamine poisoning. This is because isoniazid blocks the enzymes monoamine oxidase (MAO) and diamine oxidase (DAO) (16).

Serotonin reuptake inhibitors can give serotonin syndrome if the patient is taking these drugs and consuming grapefruit juice at the same time, a condition that manifests with high fever, chills, restlessness, sweating, and diarrhea (7,17).

Table 3 presents the most important interactions that change the pharmacodynamics of drugs with food and enable the occurrence of adverse effects.

Table 3. Pharmacodynamic food-drug interactions

Drugs	Food	Drug-Food Interaction
Warfarin	Cranberry, foods rich in omega3	Synergistic effect
Warfarin	Foods rich in vitamin E	Synergistic effect
Warfarin	Foods rich in vitamin K	Antagonistic effect
ACE-inhibitors	Foods rich in potassium	Hyperkalemia
Isoniazid	Foods rich in histidine	Histamine poisoning
MAO-inhibitors	Foods rich in tyramine and dopa	Hypertensive crisis

Fluoxetine/ trazodone	Grapefruit juice	Serotonin syndrome
Antithyroid Drugs	Iodine-Rich Foods	Antagonistic effect
Acetaminophen (paracetamol)	Alcohol	Increase liver toxicity
Insulin, Oral Diabetic Agents	Alcohol	Hypoglycemia

5. Conclusion

From the reviewed literature we can conclude that:

- ✓ There are important interactions between certain medications and foods
- ✓ These interactions can be moderate, but in some cases quite dangerous, threatening the health of patients.
- ✓ The most common interactions are pharmacokinetics, especially absorption and metabolism.
- ✓ Lower frequencies are pharmacodynamic but no less important
- ✓ Any patient who is being treated with certain medications, especially the elderly should consult their doctor and pharmacist about their diet
- ✓ Also, without consulting a doctor or pharmacist patients should not take any kind of supplement

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