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Review Article

Food-Drug Interactions

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Abstract

The effect of drug on a person may be different than expected because that drug interacts with another drug the person is taking (drug-drug interaction), food, beverages, dietary supplements the person is consuming (drug-nutrient/food interaction) or another disease the person has (drug-disease interaction). 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 lack of knowledge about the active ingredients involved in the relevant substances. Regarding food-drug interactions physicians and pharmacists recognize that some foods and drugs, when taken simultaneously, can alter the body's ability to utilize a particular food or drug, or cause serious side effects. Clinically significant drug interactions, which pose potential harm to the patient, may result from changes in pharmaceutical, pharmacokinetic, or pharmacodynamic properties. Some may be taken advantage of, to the benefit of patients, but more commonly drug interactions result in adverse drug events. Therefore it is advisable for patients to follow the physician and doctors instructions to obtain maximum benefits with least food-drug interactions. The literature survey was conducted by extracting data from different review and original articles on general or specific drug interactions with food. This review gives information about various interactions between different foods and drugs and will help physicians and pharmacists prescribe drugs cautiously with only suitable food supplement to get maximum benefit for the patient.

Keywords: Food-drug interaction; Cytochrome P450; Drug; Chelation.

Introduction

Medicines can treat and cure many health problems. However, they must be taken properly to ensure that they are safe and effective. Medications should be extremely specific in their effects, have the same predictable effect for all patients, never be affected by concomitant food or other medications, exhibit linear potency, be totally non-toxic in any dosage and require only a single dose to affect a permanent cure. However, this ideal drug is still to be discovered.[1]

Many medicines have powerful ingredients that interact with the human body in different ways. Diet and lifestyle can sometimes have a significant impact on drugs. 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. Typically, interactions between drugs come to mind (drug-drug interaction). However, interactions may also exist between drugs and foods (drug-food interactions), as well as drugs and herbs (drug-herb interactions).

These may occur out of accidental misuse or due to lack of knowledge about the active ingredients involved in the relevant substances. Interactions between food and drugs may inadvertently reduce or increase the drug effect. Some commonly used herbs, fruits as well as alcohol may cause failure of the therapy up a point of to serious alterations of the patient's health. The majority of clinically relevant food-drug interactions are caused by food-induced changes in the bioavailability of the drug.

Major side-effects of some diet (food) on drugs include alteration in absorption by fatty, high protein and fiber diets.[2] Bioavailability is an important pharmacokinetic parameter which is correlated with the clinical effect of most drugs. However, in order to evaluate the clinical relevance of a food-drug interaction the impact of food intake on the clinical effect of the drug has to be quantified as well.

The most important interactions are those associated with a high risk of treatment failure arising from a significantly reduced bioavailability in the fed state. Such interactions are frequently caused by chelation with components in food. In addition, the physiological response to food intake, in particular, gastric acid secretion, may reduce or increase the bioavailability of certain drugs.[3,4]

Drug interactions can alter the pharmacokinetics and/or pharmacodynamics of a drug. The pharmacodynamic interaction may be additive, synergistic, or antagonistic effects of a drug. Drug interactions (DIs) represent an important and widely under recognized source of medication errors.[5] The gastrointestinal absorption of drugs may be affected by the concurrent use of other

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agents that,[1] have a large surface area upon which the drug can be absorbed,[2] bind or chelate,[3] alter gastric pH,[4] alter gastrointestinal motility, or affect transport proteins such as P-glycoprotein. A reduction only in 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 sub therapeutic serum levels.[5]

Factors such as nonspecific binding, atypical kinetics, poor effector solubility, and varying ratios of accessory proteins may alter the kinetic behavior of an enzyme and subsequently confound the extrapolation of in vitro data to the human situation.[6] Coenzyme Q-10 (CoQ10) is very widely consumed by humans as a food supplement because of its recognition by the public as an important nutrient in supporting human health. It interferes with intestinal efflux transporter P-glycoprotein (P-gp) and as result food-drug interactions arise.[7]

The interaction of natural products and drugs is a common hidden problem encountered in clinical practice. The interactions between natural products and drugs are based on the same pharmacokinetic and pharmacodynamic principles as drug-drug interactions. Several fruits and berries have recently been shown to contain agents that affect drug-metabolizing enzymes.[8] Grapefruit is the most well-known example, but also sevillian orange, pomelo and star fruit contain agents that inhibit cytochrome P450 3A4 (CYP3A4), which is the most important enzyme in drug metabolism.[9]

The study of drug-drug, food-drug, and herb-drug interactions and of genetic factors affecting pharmacokinetics and pharmacodynamics is expected to improve drug safety and will enable individualized drug therapy. Drugs can show their efficacy only if administered in appropriate quantity with appropriate combination of drugs and foods and at appropriate time.

In contrast to the easy access to information on drug-drug interactions, the information about food-drug interaction is not always available conveniently. It is a difficult and complex problem to accurately determine the effects of food and nutrients on a particular drug. This article aims to help the healthcare professionals specially physicians and pharmacists and patients to become more knowledgeable about drug and food interactions.

Electronic search of literatures was conducted over a period of two months and all original research and review articles were included in this study. No literature was older than 20 years. The drugs were selected and reviewed on the basis of their general utilization pattern and realizing the need for reporting their interaction with different dietary supplements for better therapeutic use of these drugs within the recommended dose regimen.

Fruit Juices

Among all fruit juices, grape fruit juice (GFJ) possesses high interaction with almost all types of drugs. The juice modifies the body's way of metabolizing the medication, affecting the liver's ability to work the drug through a person's system. Taniguchi in 2007 reported a case of purpura associated with concomitant ingestion of cilostazol, aspirin and grapefruit juice in 79 years old man. His purpura disappeared upon cessation of grapefruit juice, although his medication was not altered. The most probable cause of his purpura is an increase in the blood level of cilostazol because of the inhibition of cilostazol metabolism by components of grapefruit juice; Taniguch.[9]

Numerous reports have documented drug interactions with GFJ that occur via inhibition of CYP3A enzymes.[10] Furanocoumarins present in GFJ inhibit the intestinal CYP 3A4 and have been shown to increase the oral bioavailability of medications that are CYP 3A4 substrates like Felodipine, midazolam, cyclosporine and raise their concentrations above toxic levels.[11]

GFJ is generally contraindicated to patients taking psychotropics and it is advised to inform patients about described interaction.[12] The in vitro data suggest that compounds present in grapefruit juice are able to inhibit the P-gp activity modifying the disposition of drugs that are P-gp substrates such as talinolol.[13] The overall exposure of some drugs can be increased by more than fivefold when taken with GFJ and increase the risk of adverse effects.[14]

With new anticonvulsants, serum iron and sodium need to be monitored. Additionally, users are advised to avoid drinking grape fruit juice within 1-2 hr(s) of taking these anticonvulsants.[15] Furanocoumarines and active bioflavonoids present in GFJ are also inhibitors of OATP and when ingested concomitantly, can reduce the oral bioavailability of the OATP substrate, fexofenadine.[16] Overall, a series of flavonoids present in GFJ are identified as esterase inhibitors, of which kaempferol and naringenin are shown to mediate pharmacokinetic drug interaction with most of the calcium channel antagonist and the statin groups of drugs such as enalapril and lovastatin due to their capability of esterase inhibition.[17]

Cholesterol-lowering agent lovastatin should be taken with food to enhance gastrointestinal absorption and bioavailability. The absorption of rosuvastatin, another anti-hyper lipidemic agent, was significantly decreased in the fed state compared with the fasting state, which suggests that rosuvastatin should be administered on an empty stomach.[18]

Simvastatin, Ezetimibe, pravastatin and fluvastatin may be taken without regards to food. However, high fiber diets may lower the efficacy of these drugs.[19] Concomitant administration of statins with food may alter statin pharmacokinetics or pharmacodynamics, increasing the risk of adverse reactions such as myopathy or rhabdomyolysis or reducing their pharmacological action. Consumption of pectin or oat bran together with Lovastatin reduces absorption of the drug, while alcohol intake does not appear to affect the efficacy and safety of Fluvastatin treatment.[20]

Warfarin

Warfarin is commonly used to treat or prevent thromboembolic events.[21] Patients taking warfarin are at particular risk of

interactions with dietary supplements, yet approximately 30% use herbal or natural product supplements on a regular basis.[22] There is a possible interaction between warfarin and a high-protein diet. The potential for increased dietary protein intake to raise serum albumin levels and/or cytochrome P450 activity has been postulated as mechanisms for the resulting decrease in international normalized ratio (INRs).[23]

Some vegetables (broccoli, Brussels sprouts, kale, parsley, spinach, and others) are high in vitamin K. Eating large quantities or making sudden changes in the amounts eaten of these vegetables, interferes with the effectiveness and safety of warfarin therapy.[24]

Eating charbroiled food may decrease warfarin activity, while eating cooked onions may increase warfarin activity.[25] Soy foods have been reported both to increase and to decrease warfarin activity.[25] The significance of these last three interactions remains unclear. The combination of warfarin administration and cranberry juice ingestion appeared to be associated with an elevated INR without bleeding in elderly patient.

A number of studies have been documented on the interaction of warfarin and cranberry juice.[26-30] Cranberry juice is a flavonoid, which has been shown to induce, inhibit, or act as a substrate for the biosynthesis of several cytochrome P-450 (CYP) isoenzymes. Specifically, cranberry juice may inhibit the activity of CYP2C9, the primary isoenzyme involved in the metabolism of S-warfarin. It was suggested that cranberry juice increased the International Normalized Ratio (INR) of patients taking warfarin, but neither clearly identified cranberry juice as the sole cause of INR elevation.[31] If warfarin sodium is ingested with leafy green vegetables, the hypoprothrombinemic effect of warfarin may be decreased and thromboembolic complications may develop.[32]

Monoamnine Oxidases

Antidepressant activity of monoamine oxidase inhibitors (MAOIs) was initially noted in the 1950s. Although older monoamine oxidase inhibitors (MAOIs) are effective in the treatment of depressive disorders, they are under-utilized in clinical practice due to main concerns about interaction with tyramine-containing food (matured cheese, red vine, ripped bananas, yogurt, shrimp paste and salami) or so called cheese reaction, since they are capable of producing hypertensive crisis in patients taking MAOIs.[33]

The first-generation MAOIs such as phenelzine and isocarboxazid were largely nonselective inhibitors of both subtypes of MAO, MAO (A) and MAO (B). These medications carried with them dietary restrictions.[34] Tyramine is an indirectly acting sympathomimetic agent, is degraded by MAO but in the presence of MAOIs, it escapes degradation and reaches the systemic circulation where it is taken up by the adrenergic neuron, leading to a hypertensive crisis.[35] However, MAOIs have been well established as an effective intervention for people with treatment-resistant depression, and transdermal formulations may provide a valuable therapeutic option and eliminate the drug-food interaction.[36]

Antihypertensive Drugs

Patients placed on anti hypertensive drugs will benefit from concomitant moderate sodium restricted diets.[23] Propranolol serum levels may be increased if taken with rich protein food. A change in diet from high carbohydrates/low protein to low carbohydrate/high protein may result in increased oral clearance. Smoking may decrease its plasma levels of by increasing its metabolism.[37] The intestinal absorption of celiprolol (beta-blocker) is inhibited when it is taken with orange juice. Hesperidin, present in orange juice, is responsible for the decreased absorption of celiprolol.[38] The absorption of ACEs inhibitors is increased when taken on an empty stomach.[39] While GFJ increases the bioavailability of felodipine (Ca2 channel blocker).[39]

Licorice extract, a common ingredient of dietary supplement contains glycyrrhizin and glycyrrhetinic acid. It is a potent inhibitor of 11- bet- hydroxyl steroid dehydrogenase, it increases excess of cortisol to mineralocorticoid receptors causing sodium retention and potassium depletion, so it may interfere with various medicines including antihypertensive and antiarrhythmic agents.[40,41] A high intake of liquorice can cause hypermineralocorticoidism with sodium retention and potassium loss, oedema, increased blood pressure and depression of the renin-angiotensin-aldosterone system.[42] Studies showed that a daily consumption of glycyrrhizic acid of 95 mg or more caused an increase in blood pressure. A practical guideline for an acceptable daily intake of glycyrrhizic acid seems to be 9.5 mg a day. This means no more than 10-30g liquorice and no more than half a cup of liquorice tea a day.[43]

Antibiotics

Antibiotics are widely prescribed in medical practice. Many of them induce or are subject to interactions that may diminish their anti-infectious efficiency or elicit toxic effects. Food intake can influence the effectiveness of an antibiotic.[44] Avoid co-administration of antibiotics with milk products which are rich sources of divalent ions, such as calcium and magnesium that complex with some antibiotics and prevent their absorption. The intake of dairy products, however, needs to be monitored and encouraged with appropriate consideration of specific antibiotics involved.[45]

A number of studies give evidence that fluoroquinolones forming slightly soluble complex with metal ions of food show reduced bioavailability.[46] Casein and calcium present in milk decrease the absorption of ciprofloxacin.[47] The effect of interaction of five fruit juices on the dissolution and absorption profiles of ciprofloxacin tablets were determined. It was found that the absorption of ciprofloxacin (500 mg) tablets can be reduced by concomitant ingestion of the GFJ.[48] Therefore, to avoid drug therapeutic failures and subsequent bacterial resistance as a result of sub-therapeutic level of the drug in the systemic circulation, ingestion of the juice with ciprofloxacin should be discouraged.[48]

Azithromycin absorption is decreased when taken with food, resulting in a 43% reduction in bioavailability.[39] Tetracycline should be taken one hour before or two hours after meals, and not taken with milk because it binds calcium and iron, forming insoluble chelates, and influencing its bioavailability.[39,49,50] The effect of milk added to coffee or black tea on the bioavailability of tetracycline was evaluated in healthy individuals. Results showed that even a little quantity of milk containing extremely small amounts of calcium severely impair the absorption of the drug, so that the presence of this metal ion should be carefully controlled in order to avoid decreasing the available tetracycline.[51]

Food-drug interactions may reduce the bioavailability of drugs taken after meals (negative food effects). However, enteric-coated tablets that start to disintegrate when they reach the middle-to-lower region of the small intestine could reduce negative food effects. Results indicated that food-drug interactions were avoided by separating the main absorption site of drugs from that of food components.[52]

Analgesics and Antipyretics

Analgesics and antipyretics are used to treat mild to moderate pain and fever. For rapid relief, acetaminophen should be taken in an empty stomach because food may slow the body absorption of acetaminophen. Co-administration of acetaminophen with pectin delays its absorption and onset.[53] NSAIDs like ibuprofen, naproxen, ketoprofen and others can cause stomach irritation and thus they should be taken with food or milk. Avoid or limit the use of alcohol because chronic alcohol use can increase the risk of liver damage or stomach bleeding.[39] The absorption of ibuprofen and oxycodone when given in the combination tablet was affected by the concomitant ingestion of food.[54]

The C_{max} and $AUC_{0\text{-alpha}}$ of ibuprofen were significantly increased after single and multiple doses of Coca-Cola, thereby indicating increased extent of absorption of ibuprofen. The daily dosage and frequency of ibuprofen must be reduced when administered with Coca-Cola.[55] Food intake did not appear to affect the extent of absorption (ie, total exposure) of oral Diclofenac potassium soft gelatin capsule at doses.[56]

Bronchiodilators

Bronchodilators like theophylline, albuterol, and epinephrine possess different effects with food. The effect of food on theophylline medications can vary widely. High-fat meals may increase the amount of theophylline in the body, while high-carbohydrate meals may decrease it. Avoid alcohol if taking theophylline medications because it can increase the risk of side effects such as nausea, vomiting, headache and irritability. Avoid eating or drinking large amounts of foods and beverages that contain caffeine (e.g., chocolate, colas, coffee, and tea) since theophylline is a xanthine derivative and these substances also contain xanthine. Hence consuming large amounts of these substances while taking theophylline, increases the risk of drug toxicity.[39] Additionally, both oral bronchodilators and caffeine stimulate the central nervous system.[57] Patients may be advised not to consume GFJ when taking theophylline, since it increases the bioavailability,[58] and monitoring of plasma theophylline levels in patients consuming GFJ might be helpful in better management of patient care.[59]

Antihistamines

Fexofenadine, loratadine, rupatadine, cimetidine cetirizine, are all antihistamines.[60] It is best to take prescription antihistamines on an empty stomach to increase their effectiveness. Rupatadine is commonly used for the management of diseases with allergic inflammatory conditions. A study indicates that concomitant intake of food with a single 20 mg oral dose of rupatadine exhibits a significant increase in rupatadine bioavailability.[61] Cimetidine is given with food to assist the maintenance of a therapeutic blood concentration. A fraction of cimetidine is absorbed in the presence of food, allowing the remaining drug to be dissolved once the gut is cleared. Thus, therapeutic levels are maintained throughout the dosing interval.[62,63] A study was conducted on a latest molecule esomeprazole (acid-reducer), and it was observe that its bioavailability was reduced when taken within 15 min before eating a high-fat meal *vs*. that while fasting. [64]

Antitubercular Drugs

Anti-tubercular drugs like isoniazid have been associated with tyramine and histamine interactions.[65] Inhibition of monoamine oxidase and histaminase by isoniazid can cause significant drug-food interactions. Food greatly decreases isoniazid bioavailability.[66] Oleanolic acid, a triterpenoid exists widely in food, medicinal herbs and other plants, has antimycobacterial activity against the Mycobacterium tuberculosis, when administered with isoniazid, it exerts synergistic effect.[67]

High fat meals decrease the serum concentration of cycloserine, a bacteriostatic anti-tubercular drug and results in incomplete eradication of bacteria.[68]

Antidiabetics

Glimepiride is an antidiabetic and a new generation sulfonylurea derivative should be administered with breakfast or the first main meal of the day. It has absolute bioavailability and the absence of food interaction guarantee highly reproducible pharmacokinetics.[69] Immediate release glipizide should be taken 30 minutes before meals. However, extended release tablets should be taken with breakfast.[70] The maximum effectiveness of acarbose, an alpha-glucosidase inhibitor is attained when the drug is taken immediately at the start of each meal (not half an hour before or after), because it delays the carbohydrate absorption by inhibiting the enzyme alpha-glucosidase.[35]

Thyroxine

Recent evidence pointed out the role of gastric acid secretion on the subsequent intestinal absorption of thyroxine in relation with the timing of food ingestion as well as with pH impairment associated to frequent gastric disorders like Helicobacter pylori infection and gastric atrophy.[71] Levothyroxine is a derivative of thyroxine. Grapefruit juice may slightly delay the absorption of levothyroxine, but it seems to have only a minor effect on its bioavailability. Accordingly, the clinical relevance of the grapefruit juice-levothyroxine interaction is likely to be small.[72]

Drug interactions may be theoretical or clinically relevant. A summary table is given to highlight some significant food-drug interactions. (Table 1)

Some may be taken advantage of, to the benefit of patients, but more commonly drug interactions result in unnecessary adverse events. Fortunately, undesirable drug interactions can be prevented. Becoming more familiar with potential drug interactions can help clinicians predict and explain a patient's response to medications.[73] Significant food effects complicate development of new drugs, especially when clinical plans require control and/or monitoring of food intake in relation to dosing. The prediction of whether a drug or drug product will show human food effect is challenging.[74]

Table 1: Summary of some significant Food-Drug Interactions

Drugs	Food	Drug-Food Interaction
WARFARIN	High-protein diet	raise serum albumin levels, decrease in international normalized ratio (INR)
	Vegetables containing vitamin k	interferes with the effectiveness and safety of warfarin therapy.
	Charbroiled	decrease warfarin activity
	Cooked onions	increase warfarin activity
	Cranberry juice	elevated INR without bleeding in elderly patient
	Leafy green vegetables	thromboembolic complications may develop
	Charbroiled	decrease warfarin activity
MONOAMNINE OXIDASES	Tyramine-containing food[1]	hypertensive crisis
PROPRANOLOL	Rich protein food	serum level may be increased
CELIPROLOL	Orange juice	the intestinal absorption is inhibited
ACES INHIBITORS	Empty stomach	absorption is increased
CA2 CHANNEL	Grape fruit juice	increases the bioavailability
ANTIBIOTICS	with milk products[2]	that complex with some antibiotics and prevent their absorption. reduced bioavailability
ACETAMINOPHEN	Pectin	delays its absorption and onset
NSAIDS	Alcohol	can increase risk of liver damage or stomach bleeding
	Beverages	the c_{max} and $auc_{0\text{-}alpha}$ significantly increased[3]
THEOPHYLINE	High-fat meal and grape fruit juice	increase bioavailability
	Caffeine	increases the risk of drug toxicity
ESOMEPRAZOLE	High-fat meal	bioavailability was reduced
CIMETIDINE, RUPATADINE	with food(any type)	increase bioavailability
ISONIAZIDE	Plantsmedicinal herbsoleanolic acid	exerts synergistic effect
CYCLOSERINE	High fat meals	decrease the serum concentration
ESOMEPRAZOLE	High-fat meal	bioavailability was reduced
CIMETIDINE, RUPATADINE	with food(any type)	increase bioavailability
ISONIAZIDE	Plantsmedicinal herbsoleanolic acid	exerts synergistic effect
CYCLOSERINE	High fat meals	decrease the serum concentration
GLIMEPIRIDE	with breakfast	absolute bioavailability
ACARBOSE,	at start of each meal	maximum effectiveness
MERCAPTOPURINE	Cow's milk[4]	reduce bioavailability
TAMOXIFEN	Sesame seeds	negatively interferes with tamoxifen in inducing regression of established mcf-7 tumor size but beneficially interacts with tamoxifen on bone in ovariectomized athymic mice
LEVOTHYROXINE	Grapefruit juice	delay the absorption[5]
GLIMEPIRIDE	with breakfast	absolute bioavailability

Antitumor Drugs

Mercaptopurine is a purine analog used for acute lymphoblastic leukemia and chronic myelogenous leukemias. Since it is inactivated by xanthine oxidase (XO), concurrent intake of substances containing XO may potentially reduce bioavailability of mercaptopurine. Cow's milk is known to contain a high level of XO. This interaction may be clinically significant. Therefore most patients should try to separate the timing of taking mercaptopurine and drinking milk.[75]

Tamoxifen is a successful anti-tumor agent. If taken with sesame seeds, it negatively interferes with tamoxifen in inducing regression of established MCF-7 tumor size but beneficially interacts with tamoxifen on bone in ovariectomized athymic mice.[76] Xue et al. had compared the influence of dietary elements on cancer progression, chemotherapy efficacy, and toxicity, particularly severe, late onset diarrhea related to irinotecan (CPT-11) treatment. They suggest that glutamine and n-3 fatty acids might be potentially useful adjuncts with CPT-11 treatment.[77]

Conclusion

A large number of drugs are introduced every year. Food-drug interactions can produce negative effects in safety and efficacy of drug therapy, as well in the nutritional status of the patient. Generally speaking, drug interactions are to be avoided, due to the possibility of poor or unexpected outcomes. Like food, drugs taken by mouth must be absorbed through the lining of the stomach or the small intestine. Consequently, the presence of food in the digestive tract may reduce absorption of a drug. Often, such interactions can be avoided by taking the drug 1 hour before or 2 hours after eating. Like drugs, foods are not tested as comprehensively so they may interact with prescription or over-the-counter drugs. The authors would suggest patients to tell their doctors and pharmacists about their food intake and dietary supplements so that interactions can be avoided.

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