DRUG FOOD INTERACTIONS IN VARIOUS THERAPIES

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ABSTRACT
The advancement in clinical research has encouraged the scientists to focus on development of the measures that could enhance the therapeutic outcome of the dosage regimen. This is being achieved by bypassing the possible interactions amongst the drugs as well as with food. Food can affect the clinical effects of the drugs by indirectly interacting with bioavailability of the drugs. The interactions can significantly result in increased therapeutic effects or failure of the medication therapy. This review has been assembled with special reference to the drug food interactions. The thread attempts to focus on interactions of food with drugs in different therapies providing relevant and concise information in this regard.

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INTRODUCTION

It is commonly mistaken that natural foods including fruits and other edibles are completely safe with no adverse effects. However the researches in the past decade has nullified this notion with explanation that the food also travels the same oral route as the medicines so they may affect the performance of certain drugs. The medicines taken with food concomitantly can result in enhanced or decreased effect of the drug therapy. It occurs when the food or dietary products have some effect on the active ingredient of that medicine.[1] These unwanted effects are subject of interest for researchers to eliminate or incorporate these effects for increased or rather (also) decreased absorption of drugs by altering the pharmacokinetic and pharmacodynamics of the drugs administered. These interactions can occur with food and dietary supplements (e.g. iron) as well.[2] Different drug therapies show different effects with food or beverages; e.g. calcium channel blocker (felodipine) have increased toxicity when taken simultaneously with alcohol, with lower blood pressure and adverse events than taken alone.[3] Another renowned example is grape fruit juice that shows significant interactions with many of the drug therapies showing an increase in the bioavailability of various drugs administered concomitantly[4, 5]. But the researches have shown that drugs pharmacokinetic as well as pharmacodynamics are not altered if given parenterally along with grape fruit juice.[6][7][8] Drug interactions can be defined as any modification in pharmacokinetics or pharmacodynamics of drug substances by food, drugs, dietary supplements and drinks as beverages, juices or alcohol.[9] The prevalence of adverse effects rises with greater number of drugs taken concomitantly. The risk increases to more than 50% with use of five drug components, increasing number of drugs used upto seven components risk raise to 80%.[10-15] The inappropriate use of medication has been contributed by the polypharmacy and self medication which increases the possibility of interactions with food as well as other medicines.[16, 17]

Drug Food Interactions

Components of interaction are food, dietary supplements and drugs. Examples are, Food

The food in stomach can delay the absorption of drugs. Such type of interactions can be prevented by changing the dosing pattern as by taking drugs two hours before or after taking meal.[18] Fibers in food products can also alter absorption pattern of drugs. Insoluble fibers (bran) and soluble fibers (pectin) decrease the absorption and bioavailability of nonsteroidal anti-inflammatory drugs (acetaminopen) and antihypertensive medications. Vegetables rich in vitamin K (green leafy; broccoli, spinach) can alter the effects of anticoagulant drugs as heparin and warfarin etc.[19]

Alcohol

The ethanol interacts with many drugs especially drugs that affect nervous system (antidepressants). Also if taken with metronidazole results in headache, palpitations, nausea and vomiting.[20]

Dietary Supplements

These include vitamins, amino acids and herbs that are supplement to food and nutrition. These he biocomponents can also interact with drugs and increase the possibility of side effects. Theophylline having xanthines when taken with large amounts of tea or coffee can result in theophylline toxicity.[2]

Mechanism

Pharmacokinetic Interactions

This type of interactions involve absorption, distribution, metabolism and elimination of drugs affected by food intake. These are not very common except the grape fruit juice that has significant effect because of the presence of cytochrome P450 (CYP3A4) system inhibitors. Thereby increase the bioavailability of drugs that are metabolized by this system. The most significant interactions results by decreasing the drug bioavailability, due to the reactions e.g. chelation or modification of the gastric acidic pH, GI motility and bile secretions. [5]The antifungal agent, griseofulvin has increased absorption with high fat meal.[21] Food can modify the metabolism of certain drugs. Citrus juices often taken in morning especially the grape fruit juice containing flavonoid compounds inhibit metabolism of drugs that are potentially metabolized by cytochrome P450. This can enhance the toxicity of these drugs.[22, 23] Monoamine oxidase inhibitors can cause hypertensive crises with increased levels of tyramine in the body. The tyramine rich food are fish, cheese and fermented products, patients taking monoamine oxidase inhibitors should avoid from these foods.[24-27] Certain foods can make urine acidic (eggs, meat and fish) or alkaline (citrus fruits, milk, vegetables). Salt content in diet affect the lithium serum level because of the competition between lithium and sodium for tubular reabsorption; low sodium food can increase serum levels of lithium by inhibiting its release.[21]

Pharmacodynamic Interactions

These interactions have a very few examples in which the drug action at receptor level are altered by food or its derivatives.[28] The physicochemical characteristics of the drug are essential in determining its action and its possibility for food interactions. The drugs within their same pharmacological class can differ in their possibilities for drug food interactions.[29]

Characteristic of Meal

The quantity and nature of the meal also affect the interactions. Example is the increased absorption and bioavailability of lipophilic drugs (albendazole) is increased when taken with high fat content. Certain drugs for cardiac patients e.g. digoxin and
lovastatin have decreased bioavailability with high fiber meal.[30] Various other drugs as labetalol, carbamazepine, mebendazole have increased absorption when given with food.[21]

Drug Food Interactions in Different Therapies

Antihypertensive Therapy

Chronic rise of blood pressure (systolic/diastolic) is known as hypertension. It is not regarded as disease but predict the probability of future cardiac vascular disease. The most common hypertension that frequently occur is essential hypertension (95%).[31, 32] The factors that contribute to the regulation of blood pressure include diet nature which involve lipids and minerals potassium, magnesium, sodium. The blood pressure is influenced by the total energy intake as well.[33] The aim of the treatment is to keep the blood pressure within the normal range i.e. 90-140mmHg.[34] The antihypertensive therapy include the following pharmacological classes i.e. α and β Blockers, Ca-Channel Blockers, ACE Inhibitors, ARBs etc. The antihypertensive drugs also uses the CYP P450 system for their metabolism so the food that alters or modify the CYP P450 can result in toxicity of these drugs or modify their therapeutic efficacy. Also the important membrane transporter, P-glycoprotein can mobilize these drugs from metabolic sites.[35-37]

Diuretic

The diuretics taken for blood pressure lowering e.g. the loop diuretic, furosemide is affected by food intake. Researches have shown that bioavailability decreases with concomitant food intake resulting in the absence of the diuresis (decrease by 16-45%).[38-42] Another diuretic agent bumetanides shows no change in bioavailability when administered with food.[38, 39] Potassium sparing diuretics are also affected by the diet rich in potassium especially those using spironolactone that can result in severe arrhythmias.[43] The intake of potassium containing foods as banana and green leafy vegetables (spinach) when taken with these diuretics can lead to hyperkalaemia.[44] Beta blockers and ACE inhibitors can also cause hyperkalaemia when given with potassium sparing diuretics by lowering the aldosterone level and cellular uptake of K⁺.[45] Hydrochlorothiazide (thiazide diuretic) have increased bioavailability with food.[46]

Calcium Channel Blockers

Concomitant administration of meal and nifedipine (tablet) decreases the possibility of side effects associated with peak plasma concentration of the drug while the efficacy of drug remain unchanged.[47-50] Nifedipine sustained release formulations have enhanced serum levels but the modified forms have no effect when taken with food.[51-53] Felodipine in sustained release form when administered with meal has increased gastric retention time and hence delayed absorption.[54] The grape fruit juice can result in toxicity of felodipine due to inhibition of the metabolism by liver (first pass effect) and doubles the heart rate.[55] Grape fruit juice do not affect the metabolism of diltiazem and verapamil which are also metabolized by cytochrome enzyme system.[5, 55, 56]

ACE Inhibitors

The simultaneous administration of food and antacids can result in decreased bioavailability and clinical effects of these agents. Angiotensin converting enzyme inhibitor, captopril has decreased clearance when taken with food also bioavailability decreases 42-56%. [57-59] Food does not affect or modify the absorption or bioavailability of lisinopril, enalapril and benazepril and can be administered at any time with or without food.[60-63] Quinapril also has unaffected absorption peak when taken along with food,[64] The therapy with ACE inhibitors may cause hyperkalaemia so the diet rich in potassium or substitution of salt should be avoided.[65, 66]

Angiotensin II Receptor Blockers (ARBs)

Meals generally do not affect the bioavailability or absorption pattern of these agents.[67] Valsartan, losartan and telmisartan have decreased bioavailability when administered with food and possess high plasma drug concentration when taken alone.[67, 68] Irbesartan and losartan are metabolized by the CYP enzyme system and hence prone to drug interactions with drugs that modify or alters the function of this system.[69] The irbesartan is not affected with food intake along its administration.[70, 71]

Lipid Lowering Agents

Bioavailability studies have shown that it increases in case of lovastatin when taken with food[72] while it decreases in case of pravastatin.[73] The intake of high fiber diet (vegetables and fruits) results in lowering of lovastatin absorption with decreased clinical efficacy.[74] Other agents bioavailability e.g. atorvastatin[75, 76] and fluvastatin[77] remains unchanged when taken with food. The toxicity and adverse effects can result by inhibition of hepatic metabolism of atorvastatin, lovastatin and simvastatin by the action of grape fruit juice flavonoids.[78-80] Whereas fluvastatin and pravastatin do not interact with citrus juice.[5, 78]

Antimicrobial Interaction with Food

Milk intake do not affect ampicillin availability.[81] The food affects ampicillin absorption decreases its bioavailability does not change and can result in therapeutic failure.[82-86] The bioavailability of amoxicillin is unaffected by milk but the high fiber food can decrease its bioavailability.[82, 85-87] The tetracycline(doxycline) interact with food, dairy products and iron supplements and can result in treatment failure due to decrease in its bioavailability that occurs by chelation of these agents with metal ions (Mg++, Ca++, Al+++).[88-91]
Some cephalosporins interact with food while others remain unaffected. Cefuroxime absorption increases with food[92-95] while in young children, cephalaxin absorption decreases[96] and remain unaffected in adults.[97, 98]

The esters of erythromycin used in formulation effects its pharmacokinetic behavior when administered with food. The researches have shown that erythromycin ethylsuccinate absorption increase in children[96, 99] but decrease in adults[100] when administered with food. Erythromycin stearate has shown to have increased absorption when taken with meal. As the bioavailability of erythromycin depends on the type of formulation and the salt used so, the enteric coated tablets and pellets remain unaffected by food in few researches[101-103] however they seemed to be affected by food in other researches.[103] It is concluded from studies regarding erythromycin drug interactions that the standard dose reduces the risk of therapeutic failure.

The quinolones interact with dairy products due to chelation[104] with the metal cations that can result in therapeutic failure especially in case of ciprofloxacin[105-108] or norfloxacin[109] but the ofloxacin[108, 110-113] does not interact with dairy products. Ciprofloxacin also has a decreased absorption when administered with food.

Antirheumatic Therapy

Methotrexate interacts with folic acid, it antagonizes the folate enzyme activity thereby resulting in many side effects including hematological abnormalities and GI intolerance; methotrexate toxicity can be induced.[114, 115] It is recommended in Japanese Guideline that folic acid should be administered with methotrexate to prevent the unwanted side effects and toxicity.[115-117] The folic acid rich diet can eliminate the methotrexate toxicity and can also end the activity of the drug.[118, 119]

The calcineurin inhibitors (tacrolimus) used in rheumatic therapy are metabolized cytochrome enzymes in liver so the diet or agents that interfere with the activity of these enzymes have effect on these agents.[120, 121] Examples of the agents that can interfere with the CYP450 system are the grape fruit juice/citrus juice. These can cause marked increase in the serum level of tacrolimus because grape fruit juice is the potent inhibitor of these enzymes.[122, 123]

Antiarhythmic Drug Interaction with Food

Lidocaine bioavailability increases when taken with food. The food also increases the hepatic clearance of lidocaine due to occupation of the enzymes responsible for the clearance of the drug.[124] Diprafenone[125] and procaainamide[126] systemic absorption increases when ingested with food but it decreases in case of flecainide when it is taken with milk.[127] Penticainide bioavailability is unaffected with food.[128]

The beta blockers taken as antiarrhythmic agents as bevantolo[129] and acebutolo[130], the bioavailability remains unaffected in the former but increases slightly in the later when taken with the food. Metoprolol availability is increased when taken with food.[131] The saturation of the first pass effect by the food in propranolol therapy has shown to increase its systemic availability.[132] Simultaneous intake of garlic has shown to increase the availability of propranolol.[133, 134] The sustained release forms of felodipine[54] are retained in stomach for longer periods of time and exhibit delayed absorption while the sustained release forms of verapamil[135, 136] has increased absorption. The systemic absorption of verapamil is unaffected by diet rich in proteins.[136]

Digoxin availability is altered by the food intake, the availability of digoxin and beta methyl digoxin is more with the fasted stomach as compared to when taken with food.[137] Amoidrone bioavailability is not affected by the high fat meal.[138]

Antifungal Therapy

The systemic absorption of griseofulvin decrease when taken with carbohydrate/protein rich meal [139] and increase with fatty meal.[140-143]

The ketoconazole administered concomitantly with food does not result in treatment failure due to sub therapeutic serum concentration of drug.[144]

The systemic absorption of itraconazole capsule is increased with food intake[145-149] while it decreases in case of solution of itraconazole.[150, 151]

Some antifungal agents like ethambutol can be taken with food as it has no interaction with food.[152, 153]

Antiviral Agents

The absorption of ganiclovir and saquinavir is increased when administered with food.[154-157]

Grape Fruit Juice Interactions with Drugs

The studies on this juice has shown that the grape fruit juice affects the intestinal enzymes and do not alter the activity of the liver cytochrome enzymes. This study has supported the research that it affects the area under plasma concentration curve but not influence the systemic elimination half life and clearance.[55] It also alters the activity of the transporter proteins specifically the P-glycoprotein. Few researches supported efflux while others suggested the inhibition of P-glycoprotein. The beta blocker talinolol absorption increases when given concomitantly with grape fruit juice because of inhibition of the cytochrome enzymes that metabolizes talinolol.

The systemic absorption is augmented by the grape fruit juice even after its 12 hour early intake prior to lovastatin administration.

Calcium channel blockers have significant interactions with this juice. The agents include felodipine, nicardipine and nisoldipine. Felodipine systemic absorption increased markedly when taken with grape fruit juice[55, 158, 159] also its metabolite dihydropyridine felodipine concentration increases in plasma.[160, 161] Nicardipine[8] and nisoldipine[162, 163] have similar effects
with grape fruit juice but the other agents as nitrendipine, pranidipine and nimodipine have only slight interaction with grape fruit juice.[164, 165]

Terfenadine concentration increases to the toxic level when given concomitantly with grape fruit juice because this antihistaminic agent is metabolized by the cytochrome enzyme system.[166, 167]

Similarly the systemic concentration of silfenadil increases when administered with this juice[168] but no effect on the area under the curve of silfenadil.[169]

The benzodiazepines diazepam[170], midazolam and triazolam[171, 172] plasma concentration increases when administered simultaneously with grape fruit juice.

**Immunosuppressive Medications**

Cyclosporine, sirolimus, tacrolimus have substantial interaction with food especially with the grape fruit juice. Grape fruit juice can cause increased serum level of cyclosporine by inhibiting its metabolism by the cytochrome system resulting in potential toxicity.[5] Sirolimus and tacrolimus can cause severe nephrotoxicity when taken with diet deficient in sodium.[173] Tacrolimus absorption decreases when taken with food.[174]

**Oral Anticoagulants Interaction with Food**

Dabigatran and rivaroxaban are the new emerging anticoagulants, they show interaction with food in research studies. By simultaneous intake of high fat and caloric breakfast dabigatran showed decreased absorption.[175, 176] The studies on rivaroxaban showed that on fed state the drug do not reach the maximum plasma concentration and resulted in the increase in the prothrombin time.[177, 178] Apxibob showed no interaction with food.[179] Warfarin interacts significantly with the vitamin K, the vitamin present in green leafy vegetables, plant oils and foods containing these oils as margarines and salad dressings. The vitamin K affects the anticoagulant activity of warfarin and hinders the successful anticoagulant activity of warfarin.[180]

**Dietary Supplement Interactions**

One of the dietary supplement used for treating depression is St. John’s Wort. It has severe interactions with indinavir decreasing its systemic concentration[181] and results in transplant rejection of heart by interacting with immunosuppressive agent, cyclosporine.[182]

Echinacea significantly affects the activity of the metabolizing enzymes of the cytochrome system thus affecting the plasma concentration of the agents that are in turn metabolized by these enzymes. Echinacea is often used to cure the viral infections and cold.[183, 184]

Similarly another dietary supplement ginkgo biloba significantly affects the cytochrome enzymes and also affects the plasma level of omeprazole and its metabolite agent 5-hydroxyomeprazole.[185, 186] Fish oil interact with warfarin and antidepressants resulting in their increased effect.[187] Garlic may cause increased risk in bleeding as well as increased hypoglycemia by interacting with antiplatelet drugs, warfarin and glyburide.[187-189] Ginseng interacts with hypoglycemic agents causing increased hypoglycemia but decrease the effect of warfarin.[187, 189]

**CONCLUSION**

The interaction of drugs with food which affect the therapeutic efficacy of the medication are most significant. Food affects the bioavailability of the drugs, either increase or decrease the systemic absorption of the therapeutic agents. The interactions resulting in increased bioavailability can result in toxicity and adverse events of drugs. Similarly those with decreased availability can cause the therapeutic failure and tolerance. Drug food interactions require monitoring and dosage regimen evaluation including counselling to the patients to achieve the desired therapeutic outcomes. The patients should be given appropriate information of potential interactions in the dosage regimen to contribute to the successful therapy. This review gives some information regarding food effects on the drug administration. The information is necessary for the health care providers, pharmacist and nursing staff to guide the patients and monitor further interactions evaluating the possible outcomes.

**REFERENCES**