Chapter 12

NUTRIENT DRUG INTERACTION

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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. 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.

Major side-effects of some diet (food) on drugs include alteration in absorption by fatty, high protein and fiber diets. 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. The gastrointestinal absorption of drugs may be affected by the concurrent use of 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.

Several fruits and berries have recently been shown to contain agents that affect drug-metabolizing enzymes. 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. The novel finding that grapefruit juice can markedly augment oral drug bioavailability was based on an unexpected observation from an interaction study between the dihydropyridine calcium channel antagonist, felodipine, and ethanol in which grapefruit juice was used to mask the taste of the ethanol. Subsequent investigations showed that grapefruit juice acted by reducing presystemic felodipine metabolism through selective post-translational down regulation of cytochrome P450 3A4 (CYP3A4) expression in the intestinal wall.

Among all fruit juices, grape fruit juice possesses high interaction with almost all types of drugs. 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.Furanocoumarins present in Grape Fruit Juice 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. Grape Fruit juice is generally contraindicated to patients taking psychotropics and it is advised to inform patients about described interaction.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

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P-gp substrates such as talinolol.Users are advised to avoid drinking grape fruit juice within 1-2 hr(s) of taking these anticonvulsants.

Furanocoumarines and active bioflavonoids present in Grape Fruit Juice are also inhibitors of OATP and when ingested concomitantly, can reduce the oral bioavailability of the OATP substrate, fexofenadine. Overall, a series of flavonoids present in Grape Fruit Juice 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.

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.Warfarin is commonly used to treat or prevent thromboembolic events. 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).

Eating charbroiled food may decrease warfarin activity, while eating cooked onions may increase warfarin activity. Soy foods have been reported both to increase and to decrease warfarin activity. 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.

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.

Patients placed on anti hypertensive drugs will benefit from concomitant moderate sodium restricted diets. 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. 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. The absorption of ACEs inhibitors is increased when taken on an empty stomach. While GFJ increases the bioavailability of felodipine (Ca2 channel blocker).

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. 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. 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.

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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. 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.

A number of studies give evidence that fluoroquinolones forming slightly soluble complex with metal ions of food show reduced bioavailability. Casein and calcium present in milk decrease the absorption of ciprofloxacin. 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. 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. Azithromycin absorption is decreased when taken with food, resulting in a 43% reduction in bioavailability. 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.

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.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. The absorption of ibuprofen and oxycodone when given in the combination tablet was affected by the concomitant ingestion of food.

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. Additionally, both oral bronchodilators and caffeine stimulate the central nervous system. Patients may be advised not to consume Grape Fruit Juice when taking theophylline, since it increases the bioavailability, and monitoring of plasma theophylline levels in patients consuming GFJ might be helpful in better management of patient care.

Fexofenadine, loratadine, rupatadine, cimetidine cetirizine, are all antihistamines. 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. 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.

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Anti-tubercular drugs like isoniazid have been associated with tyramine and histamine interactions. Inhibition of monoamine oxidase and histaminase by isoniazid can cause significant drug-food interactions. Food greatly decreases isoniazid bioavailability. 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.

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

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. Immediate release glipizide should be taken 30 minutes before meals. However, extended release tablets should be taken with breakfast. 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.

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.

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. 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.

Food-drug interactions can produce negative effects in safety and efficacy of drug therapy, as well in the nutritional status of the patient. 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. Like drugs, foods are not tested as comprehensively so they may interact with prescription or over-the-counter drugs

REFERENCES

1. Frankel EH. (2003). Basic Concepts. In: Hand book of food-drug Interactions, McCabe BJ, Frankel EH., Wolfe JJ (Eds.) pp. 2, CRC Press, Boca Raton, 2003.
2. Ayo JA, Agu H, Madaki I. Food and drug interactions: its side effects. Nutr Food Sci 2005;35(4):243-252.
3. Schmidt LE, Dalhoff K. Food-drug interactions. Drugs 2002;62(10):1481-1502.
4. Nekvindová J, Anzenbacher P. Interactions of food and dietary supplements with drug metabolising cytochrome P450 enzymes. Ceska Slov Farm 2007. Jul;56(4):165-173.

ISBN 978-93-5457-774-1

5. Hansten PD. (2004) Appendix II: important interactions and their mechanisms, In: Katzung BG. (2004). editor, 09th edn, (2004) Basic and clinical Pharmacology, McGraw hill, Boston pp 1110.
6. Itagaki, S., Ochiai, A., Kobayashi, M., Sugawara, M., Hirano, T., Iseki, K.(2008). Interaction of Coenzyme Q10 with the Intestinal Drug Transporter P-Glycoprotein. J Agric Food Chem. 27; 56(16):6923-7.
7. Joshi R, Medhi B. Natural product and drugs interactions, its clinical implication in drug therapy management. Saudi Med J 2008. Mar;29(3):333-339.
8. Molden E, Spigset O. Fruit and berries–interactions with drugs. Tidsskr Nor Laegeforen 2007. Dec;127(24):3218-3220.
9. Kirby BJ, Unadkat JD. Grapefruit juice, a glass full of drug interactions? Clin Pharmacol Ther 2007. May;81(5):631-633.
10. Pawełczyk T, Kłoszewska I. Grapefruit juice interactions with psychotropic drugs: advantages and potential risk. Przegl Lek 2008;65(2):92-95.
11. de Castro WV, Mertens-Talcott S, Derendorf H, Butterweck V. Grapefruit juice-drug interactions: Grapefruit juice and its components inhibit P-glycoprotein (ABCB1) mediated transport of talinolol in Caco-2 cells. J Pharm Sci 2007. Oct;96(10):2808-2817.
12. Genser D. Food and drug interaction: consequences for the nutrition/health status. Ann Nutr Metab 2008;52(Suppl 1):29-32.
13. Ellsworth AJ, Witt D, Dugdale D. (2000), Mosby's Medical drug reference, 1999-2000. Mosby and Co. Inc., St. Louis. pp 918-919.
14. Dresser GK, Bailey DG, Leake BF, Schwarz UI, Dawson PA, Freeman DJ, et al. Fruit juices inhibit organic anion transporting polypeptide-mediated drug uptake to decrease the oral availability of fexofenadine. Clin Pharmacol Ther 2002. Jan;71(1):11-20.
15. Li P, Callery PS, Gan LS, Balani SK. Esterase inhibition by grapefruit juice flavonoids leading to a new drug interaction. Drug Metab Dispos 2007. Jul;35(7):1203-1208.
16. Li Y, Jiang X, Lan K, Zhang R, Li X, Jiang Q. Pharmacokinetic properties of rosuvastatin after single-dose, oral administration in Chinese volunteers: a randomized, open-label, three-way crossover study. Clin Ther 2007. Oct;29(10):2194-2203 10.1016/j.
17. McCabe BJ, Frankel EH, Wolfe JJ. (2003). Monitoring nutritional status in drug regimens. In: Hand book of food-drug Interactions, McCabe BJ, Frankel EH., Wolfe JJ (Eds.). CRC Press, Boca Raton. pp 73-108.
18. Vaquero MP, Sánchez Muniz FJ, Jiménez Redondo S, Prats Oliván P, Higueras FJ, Bastida S. Major diet-drug interactions affecting the kinetic characteristics and hypolipidaemic properties of statins. Nutr Hosp 2010. Mar-Apr;25(2):193-206.
19. Paeng CH, Sprague M, Jackevicius CA. Interaction between warfarin and cranberry juice. Clin Ther 2007. Aug;29(8):1730-1735 10.1016/j.clinthera.
20. Wittkowsky AK. Dietary supplements, herbs and oral anticoagulants: the nature of the evidence. J Thromb Thrombolysis 2008. Feb;25(1):72-77.

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