Effects of Food Intake

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The management of many diseases requires drug treatment, particularly involving the use of multiple drugs. Food-drug interactions can affect or even change the effects of drugs, and the therapeutic effects or side effects of medications can affect the nutritional status. Alternatively, the diet and the use of supplements or the nutritional status of the patient can decrease a drug's efficacy or increase its toxicity.

The terms drug-nutrient interaction and food-drug interaction are often used interchangeably. In fact, drug-nutrient interactions are some of the many possible food-drug interactions. Drug-nutrient interactions include specific changes to the pharmacokinetics of a drug caused by a nutrient(s) or changes to the kinetics of a nutrient(s) caused by a drug. A food-drug interaction is a broader term that also includes the effects of a medication on nutritional status. Nutritional status may be impacted by the side effects of a drug, which could include an effect on appetite or the ability to eat. Food-drug interaction studies are important to evaluate appropriate dosing, timing, and formulation of new drug candidates. It is crucial that healthcare professionals take into consideration the drug-nutrient interactions in order to optimize the effectiveness and minimize the toxicities of medications.

Awareness of these interactions enables the healthcare professional and patient to work together to avoid or minimize problems (Table 1).

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Table 1 Benefits of minimizing drug interactions. (Adapted from Pronsky 2004)

Medications achieve their intended effects
Patients do not discontinue their drugs
The need for additional medication is minimized
Fewer caloric or nutrient supplements are required
Adverse side effects are avoided
Optimal nutritional status is preserved
Accidents and injuries are avoided
Disease complications are minimized
The cost of healthcare services is reduced
There is less professional liability

Pharmacological Aspects of Food-Drug Interactions

Medication is administrated to produce a pharmacological effect in the body or, more specifically, in a target organ or tissue. To achieve this goal, the drug must move from one site of administration to the bloodstream and eventually to the site of drug action. In due course, the drug may be changed to activate or inactivate metabolites and ultimately eliminated from the body. An interaction between the drug and food, a food component, or a nutrient can alter this process at any point. Food-drug interactions may be divided into two broad types: (1) **pharmacodynamic interactions**, which affect the pharmacological action of the drug, and (2) **pharmacokinetic interactions**, which affect the movement of the drug into, around, or out of the body.

Risk Factors for Food-Drug Interactions

Patients must be assessed individually for the effect of food on drug action and the effect of drugs on nutritional status. Interactions can be caused or complicated by **polypharmacy**, nutritional status, genetics, underlying illness, special diets, nutritional supplements, tube feeding, herbal or phytonutrient products, alcohol intake, drugs of abuse, nonnutrients in food, excipients in drugs or food, allergies, or intolerances. Poor patient's compliance and physician's prescribing patterns further complicate the risk. It is well established that in older people food-drug interactions could often occur due to taking of multiple drugs (prescribed and over-the-counter). In this age group, the risk of such interactions is higher than in young patients. All this is a result of physical changes related to aging such as an increase in the ratio of fat tissue to lean body mass, a decrease in liver mass and blood flow, an impairment of kidney and liver functions, illness, and endocrine and cognitive dysfunctions. Malnutrition and dehydration affect pharmacokinetics. It is known that the use of herbal and/or phytonutrient products has increased significantly by older people.

Central nervous system adverse effects of drugs can interfere with the ability or desire to eat. Recognition of these problems as a drug side effect, rather than a consequence of disease or aging, is often overlooked. It is important to evaluate the intake of nutrients that could interact when a specific medication is used. These could be vitamin K with warfarin, calcium and vitamin D with alendronate, and potassium, sodium, and magnesium with loop diuretics as furosemide.

Pharmacogenomics

Pharmacogenomics is defined as "genetically determined variations that are revealed solely by the effects of medications" (Tischio 1995). A well-known examples of a food-drug interaction ramification are G6PD (glucose-6-phosphate dehydrogenase) enzyme deficiency, warfarin resistance, and slow inactivation of isoniazid or phenelzine.

Acetylation is a conjugation reaction that metabolizes and inactivates amines, hydrazines, and sulfonamides. There are two types of acetylators: the "slow acetylators" who metabolize these medications more slowly than average due to inherited lower levels of the hepatic enzyme acetyl transferase. As a result, the unacetylated drug levels stay higher for long periods of time; the "rapid acetylators" show the opposite pattern of metabolization (Zastrow 2012). The half-life of isoniazid for rapid

acetylators is about 70 min, whereas the half-life for slow acetylators is more than 3 h (Roth 1995). More importantly, a dose prescribed normally for rapid acetylators could be toxic for slow acetylators. Thereafter, the elevated blood levels of affected drugs on slow acetylators increase the potential risk for food-drug interactions. Slow inactivation of phenelzine, a monoamine oxidase (MAO) inhibitor, increases the risk for hypertensive crisis if foods high in tyramine (e.g., cheese) are used. Dapsone and hydralazine are also metabolized by acetylation and affected by inherited differences in acetylase enzymes.

Another example is the deficiency of G6PD which is an X-chromosome-linked deficiency of G6PD enzyme in red blood cells. It is demonstrated that it can lead to neonatal jaundice, hemolytic anemia, or acute hemolysis. It is called favism, and it is generally common in African, Middle Eastern, and Southeast Asian populations. Fava beans or pollen could cause acute hemolysis in some G6PD-deficient persons, particularly those of Mediterranean origin. Aspirin, sulfonamides, and antimalarial drugs can cause hemolysis and acute anemia. Rees et al. (1993) demonstrated acute hemolysis induced in G6PD deficiency due to high doses of vitamin K or vitamin C.

Effects of Food on Drug Treatment

Drug Absorption

It has been well demonstrated that the presence of food in the stomach or lumen of the intestinal tract increases the risk to reduction of drug absorption. The absorption of alendronate and risedronate (anti-osteoporosis drugs) is almost negligible if these medications are coadministrated with food, particularly with coffee or orange juice.

The absorption of the iron from supplements can be declined by 50% when coadministrated with food. It is prescribed to take iron with 200 ml of water on an empty stomach. There are several food or nutrients that could affect iron absorption. Thus, iron should not be taken together with bran, eggs, high-phytate foods, fiber supplements, tea, coffee, dairy products, or calcium supplements.

Various mechanisms may contribute to the decrease in the rate or extent of drug absorption in the presence of food or nutrients. The presence and type of meal or food ingested influence the rate of gastric emptying. Gastric emptying could be delayed by the consumption of high-fiber meals and meals with high fat content. In general, a delay in drug absorption is not clinically significant as long as the extent of absorption is not affected. Absorption of antibiotics or analgesics may be clinically significant problems with delayed absorption. Chelation reactions occur between certain drugs and divalent or trivalent cations such as iron, calcium, magnesium, zinc, or aluminum. As a result, the absorption of drugs could be reduced by chelation with one of these ions. A well-known example is the antibiotics ciprofloxacin and tetracycline which form insoluble complexes with calcium in dairy products; calcium, magnesium, zinc, or iron supplements; or aluminum in antacids (Neuhofel et al. 2002). To minimize these interactions, it is advisable to give the drug at least 2 h before 6 h after the mineral administration.

Adsorption or adhesion to food or a nutrient is another mechanism by which drug absorption is altered. For example, a high-fiber diet could decrease the absorption of amitriptyline (a tricyclic antidepressant). Thus, the therapeutic effect is affected because of the adsorption of the drug to the fiber. It was established that digoxin, a cardiovascular drug, should not be coadministrated with wheat bran or oatmeal, both high-phytate foods.

Gastrointestinal pH is an important factor for drug absorption. Any situations that alter the gastric pH (e.g., achlorhydria or hypochlorhydria) may decrease drug absorption. An example is the defect of ketoconazole to treat *Candida* infection in patients with human immunodeficiency virus (HIV). Ketoconazole achieves best absorption in an acid medium. Welage et al. (1995) showed that achlorhydria is a common status in HIV patients, and ketoconazole tablets could not be dissolved leading to impaired drum absorption and no efficacy. This is also a concern in patients with hypochlorhydria, who are taking antacids,

histamine 2 receptor antagonists (famotidine), or proton-pump inhibitors (omeprazole). It was established that ketoconazole taken together with acid-containing beverage (cola) may improve bioavailability in these patients.

The presence of food in the stomach could alter the absorption of some drugs. The antibiotic cefuroxime axetil and the antiretroviral drug saquinavir are prescribed to be taken after a meal to reach an effective level.

Drug Distribution

Albumin is the most important drug-binding protein in the blood. Low serum albumin levels, often the result of inadequate protein intake and poor nutrition, provide fewer binding sites for highly protein-bound drugs. Fewer binding sites mean that a larger free fraction of drug will be present in the serum. Only the free fraction (which is unbound) of a drug is able to exert a pharmacologic effect at the target organ. Patients with albumin levels below 3.0 g/dl are at increased risk for adverse effects from highly protein-bound drugs. Usual adult doses of highly protein-bound drug in such patients may produce more pronounced pharmacologic effects than the same dosage in persons with normal albumin levels. A lower dose of such drug is recommended in patients with low albumin levels.

Anticoagulant warfarin, which is 99.9% serum protein bound, and anticonvulsant phenytoin, which is greater than 90% protein bound, are common drugs used in older individuals. Low albumin levels tend to be more common in elderly. In the case of warfarin, higher levels of free drug lead to risk of excessive anticoagulation and bleeding. Phenytoin toxicity can result from higher levels of free phenytoin.

Drug Metabolism

Enzyme systems in the intestinal tract and the liver, although not the only sites of drug metabolism, account for a large portion of the drug-metabolizing activity in the body. Food can both inhibit and enhance the metabolism of medication by altering the activity of these enzyme systems. A diet high in protein and low in carbohydrates can increase the hepatic metabolism on the antiasthma drug theophylline. The suspected mechanism of increased clearance of this drug is the induction of the hepatic enzyme system responsible for metabolizing the drug (Walter-Sack and Klotz 1996).

Grimm et al. (2018) have demonstrated that Grapefruit juice can cause slower gastric emptying and increase intestinal filling and thus could potentially affect drug pharmacokinetics (enhanced or altered absorption). A substance found in grapefruit and grapefruit juice can inhibit the intestinal metabolism of drugs such as calcium channel antagonists that are dihydropyridine derivatives (Bailey et al. 1994) and/or some HMG-CoA reductase inhibitors such as Simvastatin (Lilja et al. 2000). Grapefruit inhibits the cytochrome P-450 3A4 enzyme system responsible for the oxidative metabolism of many orally administrated drugs. The interaction appears to be clinically significant for drugs with low oral bioavailability, which are substantially metabolized and inactivated in the intestinal tract by the cytochrome P-450 3A4 enzyme in the intestinal wall. When grapefruit juice is ingested, the metabolizing enzyme is irreversibly inhibited, which reduces the normal metabolism of the drug. This reduction in metabolism allows more of the drug to reach the systemic circulation, and the increase in blood levels of unmetabolized drug results in a greater pharmacologic effect and possible toxicity. Unfortunately, the effects of grapefruit on intestinal cytochrome P-450 last up to 72 h, until the body can reproduce the enzyme (Lilja et al. 2000). Thus, separating the ingestion of the grapefruit and the drug does not appear to alleviate the interaction. Kogure et al. (2014) developed a method that could predict the AUC ratio, along with its interindividual variation, from the pharmacokinetic profile in the absence of grapefruit juice. This tool could be used in the daily medical practice. The grapefruit juice-calcium channel blocker interaction has been known since 1989. This interaction is related to both flavonoid and nonflavonoid components of grapefruit juice

interfering with enterocyte CYP3A4 activity. In the process, presystemic clearance of susceptible drugs decreases and bioavailability increases. The most prominent interaction occurs with felodipine (Sica 2006).

Another well-known example is the Seville oranges which are used in some marmalades, but not in commercial orange juice production; pomelos and tangelos may also cause similar reactions (Egashira et al. 2003; Malhotra et al. 2001). The interaction is not significant in drugs that are not metabolized by cytochrome P-450 3A4 in the intestinal wall, such as the HMG-CoA reductase inhibitors pravastatin and fluvastatin.

Competition between food and drugs such as propranolol and metoprolol for metabolizing enzymes in the liver may alter the first-pass metabolism of these medications. Drugs absorbed from the intestinal tract by the portal circulation are first transported to the liver before they reach the systemic circulation. Because many drugs are highly metabolized during the first pass through the liver, only a small percentage of the original dose is actually available to the systemic circulation and the target organ. When food and drug compete for the same metabolizing enzymes in the liver, more of the drug is likely to reach the systemic circulation, which can lead to toxic effect if the dose of the drug is titrated to an optimal level in the fasting state.

Drug Excretion

Food and nutrients can alter the reabsorption of drugs from the renal tubule. Reabsorption of the antimanic agent lithium is closely associated with the reabsorption of sodium. When sodium intake is low or when a patient is dehydrated, the kidneys will reabsorb more sodium. In the person treated with lithium, the kidney will reabsorb lithium as well as sodium under these conditions. Higher Lithium levels and possible toxicity will result. When excess sodium is ingested, the kidneys will eliminate more sodium in the urine and likewise more lithium. This will produce lower lithium levels and possible therapeutic failure.

Drugs that are weak acids or basis are reabsorbed from the renal tubule into the systemic circulation only in nonionic state. An acidic drug is largely in the nonionic state in the urine with an acidic pH, whereas a basic drug is largely in a nonionic state in the urine with an alkaline pH. A change in urinary pH by food may change the amount of drug existing in the nonionic state. In this way, this increases or decreases the amount of drug available for tubular reabsorption. Foods such as milk, most fruits (including citrus fruits), and most vegetables are urinary alkalinizers. The interaction is most likely to be clinically significant when the diet is composed exclusively of a single food or food group. Patients should be advised by a healthcare professional if one starts a fad diet.

Food or nutrients can alter the intended pharmacological action of a medication by enhancing the medication effects or by opposing it. The classic example of such changed drug effect is the interaction between the monoamine oxidase inhibitors (MAOIs) and neurotransmitters such as dopamine, histamine, and tyramine. These biologically active amines are normally present in many foods. They are rapidly deaminated by MAO and diamine oxidases. Inhibition of MAO by medication prevents the breakdown of tyramine and other pressor agents. Tyramine is a vasoconstrictor and, thus, raises blood pressure. It was established that a high consumption of food containing tyramine (e.g., cheeses and meats) together with MAOI antidepressants could potentially cause a hypertensive crisis and even death (Gardner et al. 1996).

Another example is caffeine in foods and beverages which increases the side effects of stimulant drugs such as methylphenidate, amphetamines, and theophylline. This interaction results in nervousness, tremor, and insomnia. In addition, caffeine could oppose or even interact the anti-anxiety effect of tranquilizers (e.g., lorazepam).

Warfarin is an oral anticoagulant which mechanism of action is to reduce the hepatic production of vitamin K-dependent clotting factors. In order to achieve an optimal level of anticoagulation, a balance should be maintained between the dose of the drug and the ingestion of vitamin K. It is mandatory to counsel a person taking warfarin to

prohibit to consumption of high vitamin K foods such as dark green, leafy vegetables (Booth et al. 1997). It was established that the ingestion of other foods or ingredients could also alter the anticoagulant effect of warfarin. Such ingredients are found in onions, garlic, vitamin E supplements in doses greater than 400 UI, and certain herbal products (dong quai, which contains coumarin-like substances, and ginseng which has an anti-platelet activity).

Alcohol

It is well-known that Ethanol together with certain medications will produce additive toxicity which could affect various organs and systems. One of the examples is the combination between ethanol and central nervous system (CNS) depressant medications such as benzodiazepines (diazepam, etc.) and barbiturates. This interaction leads to excessive drowsiness, incoordination, and other signs of CNS depression. Ethanol irritates the stomach mucosa. It was demonstrated that combining ethanol with agents that can cause the same side effects such as the nonsteroidal anti-inflammatory drugs, and particularly aspirin, will increase the risk of gastrointestinal ulceration and bleeding. Drugs that exert hepatotoxic effect (acetaminophen, amiodarone, methotrexate) should not be coadministrated with ethanol due to its high hepatotoxic potential (Lieber 1994). It is established that ethanol inhibits the gluconeogenesis in the liver and particularly when administrated in the fasting state. This leads to prolonged hypoglycemia and thus should not be taken together with insulin or oral antidiabetic drugs. The coadministration of ethanol with disulfiram could potentially lead to life-threatening disulfiram reaction characterized by rapid heartbeat, flushing, palpitations, and elevation of blood pressure. Disulfiram inhibits the acetaldehyde dehydrogenase, an enzyme which catabolizes ethanol in the liver. As a result an increase of acetaldehyde presents in the blood, and within 15 min of alcohol consumption, symptoms of flushing, nausea, and headache occur. These unpleasant effects of disulfiram are commonly used in the treatment of alcoholism or prevention of alcoholics to return to drinking. Other drugs when coadministrated with ethanol could lead to disulfiram-like reactions. These drugs are some antibiotics such as metronidazole and cefoperazone, the oral hypoglycemic drug chlorpropamide, and the antineoplastic agent procarbazine.

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