Drug-Nutrient Interactions

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Drug-nutrient interactions are a commonly overlooked aspect of the prescribing practices of physicians. As more pharmaceutical agents become available, attention should be focused on interactions of drugs with foods and nutrients. Although drug-nutrient interactions are not as common as drug-drug interactions, they can have an impact on therapeutic outcome. Drugs can affect nutritional status by altering nutrient absorption, metabolism, utilization or excretion. Food, beverages and mineral or vitamin supplements can affect the absorption and effectiveness of drugs. Knowledge of drug-nutrient interactions can help reduce the incidence of these effects. Physicians should question patients about their dietary habits so that patients can be informed about possible interactions between a prescribed drug and foods and nutrients.

Over the past few years, an increased amount of attention has been given to the interaction of drugs with certain foods. Factors that can increase the potential for interactions include long-term drug administration, poor dietary intake, preexisting disease states (especially gastrointestinal disease), increased nutritional needs due to recent surgery or infection, and the patient's age (very young or very old).

Nutritional status and diet can affect the action of drugs by altering absorption, distribution, metabolism and excretion. Nutritional status may also influence drug response. Conversely, drugs can alter nutrient absorption, metabolism, utilization and excretion. The effect of these interactions may result in altered nutritional status.

Evidence thus far has indicated that nutritional status is an important determinant of drug response and that dietary modifications are essential in patients who are at nutritional risk. Nutritional risk is often identified by the presence of two or more of the following criteria: 82 percent or less of the ideal body weight; a serum albumin of 35 g per L (3.5 g per dL) or less; a total lymphocyte count of 1.800 cells per mm^3 (1.8×10^9 per L) or less, and unintentional rapid weight loss of greater than 5 percent of body weight within one month.

Drug-nutrient interactions can be categorized into three groups: effect of drugs on nutritional status, drug-food incompatibilities and drug-alcohol incompatibilities. Table 1 lists the most commonly prescribed drugs that are associated with potential drug-nutrient interactions.

Effect of Drugs on Nutritional Status

Nutrient Absorption

Drug-induced alterations in nutrient absorption may be primary or secondary. Primary drug-induced malabsorption is due to the direct effects of the pharmacologic agent on the intestinal mucosa or on the intraluminal processes. Secondary drug-induced malabsorption is due to preexisting poor physiologic status.

Table 1. Commonly Used Drugs Associated with Nutrient Interactions

Alprazolam
Special instructions for administration
Dietary precautions

Alprazolam (Xanax)
No alcohol
Amitriptyline (Elavil, Endep)
Take with food
Limit alcohol
Amoxicillin
May take with water, fruit juice, milk or carbonated beverages
Captopril (Capoten)
Take 1 hour before meals
No potassium salt substitute
Cefaclor (Ceclor)
Take on empty stomach
No alcohol
Cimetidine (Tagamet)
Take with food
Limit caffeine; no alcohol
Cyclobenzaprine (Flexeril)
Limit alcohol
Digoxin (Lanoxin)
Take with water 30 minutes before or 2 hours after food
Diet: high potassium and magnesium, and low sodium; no natural licorice
Diltiazem (Cardizem)
Take 1 hour before or 2 hours after meals
Limit alcohol
Dipyridamole (Persantine)
Take with water on empty stomach
Erythromycin base or stearate
Take on empty stomach
Erythromycin estolate

Take with meals but not milk

Estrogens

Take with or after food to minimize nausea

Sodium-restricted diet

Glipzide (Glucotrol)

Take 30 minutes before breakfast

Follow appropriate diet; no alcohol

Glyburide (DiaBeta, Micronase)

Take with breakfast or first main meal

Follow appropriate diet; no alcohol

Hydrochlorothiazide (Esidrex, HydroDIURIL, Oretic, etc)

Take with breakfast or high-potassium food

Diet: high potassium, low sodium, may need potassium supplement; no natural licorice; limit alcohol

Isotretinoin (Accutane)

Limit alcohol; no vitamin A supplements

Lorazepam (Ativan)

Avoid alcohol; limit caffeine

Lovastatin (Mevacor)

Take with evening meal

Follow appropriate diet

Metoprolol (Lopressor)

Take with food

Diet: low sodium and low calcium

Nitroglycerin

Take on empty stomach

No alcohol

Nonsteroidal anti-inflammatory drugs

Take with food or milk

No alcohol

Phenytoin (Dilantin)

Take with food or after meals to reduce gastric irritation

If vitamin B_6 or folic acid is needed, administer cautiously

Potassium chloride

Take with food; dilute or dissolve in 4 oz water or juice

Propoxyphene napsylate with acetaminophen (Darvocet-N 100)

Limit alcohol; avoid high-protein diet

Propranolol (Inderal)

Take with food

Diet: low sodium and low calcium

Tetracycline

Take with 8 oz water on empty stomach 1 hour before or 2 to 3 hours after meals

Avoid dairy products and iron preparations for 2 to 3 hours after taking drug

Theophylline

Take with food

Limit caffeine; do not change carbohydrate or protein intake; no charcoal-broiled meats

Thyroid preparations

Take on empty stomach

Avoid cabbage, kale and brussels sprouts

Triamterene (Dyrenium)

Take with or after breakfast

Avoid potassium supplements, potassium salt substitutes and potassium-rich foods

Triazolam (Halcion)

Take at bedtime

No alcohol

Verapamil (Calan, Isoptin)

Take on empty stomach

Limit alcohol

Warfarin (Coumadin, Panwarfin)

Avoid fad diets or high consumption of vitamin K foods (green leafy vegetables); avoid excessive amounts of onions and garlic; limit alcohol and caffeine.

Prolonged use of stimulant laxatives, such as bisacodyl (Dulcolax, Fleet), increases the rate of transit and reduces the absorption of glucose, protein, sodium, potassium and some vitamins. Excessive use of phenolphtalein-containing laxatives decreases vitamin D and calcium absorption. Mineral oil acts as a physical barrier and a solvent for fat-soluble vitamins, leading to malabsorption of carotene, vitamins A, D, E and K, calcium and phosphorus.

The aluminum in aluminum hydroxide gel can combine with phosphorus to form an insoluble complex that is excreted in the feces. This feature is valuable in the management of hyperphosphatemia. On the other hand, phosphate depletion may result when the diet is low in phosphate. Aluminum-containing antacids can precipitate bile acids, leading to decreased absorption of vitamin A.

Bile acid sequestrants, such as cholestyramine (Cholybar, Questran) and colestipol (Colestid), decrease the serum cholesterol level by preventing reabsorption of bile acids, thereby increasing the rate of conversion of cholesterol to bile acids. Binding of bile acids, however, can result in deficiencies of iron, folic acid and fat-soluble vitamins such as vitamin A. Liver stores of fat-soluble vitamins are usually sufficient for a time, but a vitamin supplement may be needed for long-term therapy.

Sulfasalazine (Azulfidine), which is used to treat ulcerative colitis, inhibits intestinal transport of folic acid. To prevent folic acid deficiency in patients receiving sulfasalazine, a balanced diet with foods high in folic acid should be recommended rather than supplements.

Broad-spectrum antibiotics destroy intestinal flora that synthesize vitamin K. Vitamin K deficiency can then lead to bleeding in patients with hypoprothrombinemia. This condition can

be easily reversed by treatment with oral or parenteral vitamin K.

Nutrient Metabolism and Utilization

Drugs that alter nutrient metabolism and utilization do so by two mechanisms: (1) enhanced metabolism and excretion of vitamin D, causing a decrease in calcium absorption, and (2) interference with folic acid metabolism, creating the potential for megaloblastic anemia.

Anticonvulsants such as phenytoin (Dilantin), phenobarbital and primidone (Mysoline) induce the hepatic cytochrome P-450 microsomal mixed-function oxidase, leading to accelerated metabolism of vitamin D. Because vitamin D is necessary for calcium absorption, a decrease in vitamin D may be accompanied by a decrease in calcium absorption. Osteomalacia and rickets may occur in epileptic patients who are taking these anticonvulsants. In most patients, however, adequate dietary intake of vitamin D obviates the need for vitamin D supplementation. These anticonvulsants also utilize folic acid as a cofactor during enzyme induction, which can lead to clinical folate deficiency states. However, folic acid supplementation may lead to reduce serum levels of anticonvulsants and decreased anticonvulsants efficacy.

Methotrexate, pyrimethamine (Daraprim), nitrofurantoin (Furadantin, Macrodantin) and trimethoprim are all drugs that act as folic acid antagonists. They bind to dihydrofolate reductase and prevent the conversion of folic acid and dihydrofolate to its active form, tetrahydrofolate, which is required for purine synthesis. Although the risk of folic acid deficiency is rare with these agents, caution must be exercised in patients who already have depleted folate stores. If megaloblastic anemia occurs, folic acid supplementation is required for treatment.

Isoniazid (Laniazid) and hydralazine (Alazine, Apresoline) bind and inactivate pyridoxine (vitamin B_6), which may result in pyridoxine deficiency and peripheral neuropathy. A pyridoxine dosage of 50 to 100 mg daily is sufficient to prevent peripheral neuropathy.

Nutrient Excretion

Loop and thiazide diuretics increase urinary excretion of sodium, potassium and magnesium. Loop diuretics increase urinary excretion of calcium, whereas thiazide diuretics actually decrease it. Potassium supplementation is often required to prevent hypokalemia and digitalis toxicity in patients taking digoxin (Lanoxin). Patients with renal failure should be evaluated before they are given potassium supplements. Patients should be advised to consume foods rich in potassium and magnesium and low in sodium, and to take the potassium supplement in the morning with foods that are high in potassium.

Chronic high-dose aspirin therapy, 4 to 5 g per day, can lead to increased ascorbic acid excretion and potassium depletion. Alcohol should be avoided, since it enhances the ulcerogenic effect of aspirin. Iron deficiency anemia can result from microhemorrhages and subsequent blood loss. Patients taking aspirin chronically, especially those who are receiving large doses for the treatment of rheumatoid arthritis, should consume foods high in iron and vitamin C.

Fluid and Electrolyte Balance

Sodium and water retention are common side effects of steroids, certain antihypertensive drugs and nonsteroidal anti-inflammatory drugs (NSAIDs). Diuretic therapy and dietary sodium restriction may be beneficial to counteract the adverse effects of these agents.

Fluid and electrolyte imbalances can result from corticosteroid administration. The duration of therapy, the dose, the patient's age and preexisting illness are factors that must be taken into consideration when monitoring electrolyte levels. Weight gain is usually due to fluid retention. Steroids also tend to increase appetite, contributing to further weight gain. Patients should be counseled to be aware of this side effect. Chronic high-dose steroids can produce osteoporosis and osteopenia by reducing the level of 1,25-dihidroxycholecalciferol, which leads to decreased calcium absorption. Since glucocorticoids can induce gluconeogenesis, resulting in a negative nitrogen balance, increased dietary protein intake is important to help maintain a positive nitrogen balance.

Fluid retention and weight gain are common adverse effects of several antihypertensive agents, such as guanadrel (Hylorel), nifedipine (Adalat, Procardia) and terazosin (Hytrin). The use of diuretics in the management of hypertension can aid in reducing fluid retention. Patients should be encouraged to reduce their weight, exercise and adhere to a low-salt diet while taking antihypertensive medications.

Effect of Diet on Drugs

Food, beverages and mineral or vitamin supplements can affect the pharmacokinetics of a drug. Drug response can be significantly altered by the ingestion of certain foods. Patients should be made aware of which foods they should avoid and which they should eat more of while taking certain drugs.

Drug Absorption and Bioavailability

Foods can decrease, delay or increase the absorption of drugs by altering bioavailability, solubility in gastric fluid or gastric emptying time. A delay in drug absorption does not necessarily mean that less drug is absorbed, but peak blood levels of the drug may take longer to achieve.

Inactive complexes can result from drugs that bind to nutrients, rendering both the drug and the nutrient unavailable for absorption. The most common interactions involve tetracycline and divalent and trivalent cations, which are present in milk, dairy products, iron preparations and antacids. These products should be avoided for two hours after taking tetracycline. Another interaction involves the binding and decreased absorption of folic acid by cholestyramine, which may result in folic acid deficiency.

Food generally delays, but does not ultimately decrease, the absorption of the following drugs: acetaminophen, amoxicillin, aspirin, cefaclor (Ceclor), cephalexin (Keflex), cephradine (Anspor, Velosef), cimetidine (Tagamet), digoxin, furosemide (Lasix), metronidazole (Flagyl), potassium and sulfisoxazole (Gantrisin). High-fiber diets containing bran delay the absorption of digoxin but do not affect its bioavailability. Patients should be instructed to avoid high-fiber foods for two hours after taking digoxin.

Food decreases the absorption of the following drugs: ampicillin, doxycycline (Vibramycin), tetracycline, erythromycin stearate, isoniazid, rifampin (Rifadin, Rimactane), levodopa (Dopar, Larodopa), penicillin G and VK suspensions, nafcillin (Unipen) and phenobarbital. Patients taking these drugs should be instructed to take the drugs on an empty stomach (ie, one hour before or two hours after a meal).

Food can increase the absorption of drugs by several mechanisms. High-fat meals increase the absorption of lipophilic drugs such as griseofulvin (Grisactin, Fulvicin). Propranolol (Inderal) and metoprolol (Lopressor) are extensively metabolized during first-pass hepatic extraction. Food can increase absorption of these drugs by decreasing first-pass metabolism. High-carbohydrate meals can decrease gastric emptying time, leading to increased absorption of hydrochlorothiazide (Esidrix, HydroDIURIL, Oretic, etc), nitrofurantoin and propoxyphene (Darvon). Food also increases the absorption of hydralazine, spironolactone (Aldactone), carbamazepine (Tegretol), diazepam (Valium), and erythromycin estolate and ethylsuccinate.

Drug Metabolism

Drugs are metabolized by two basic reactions. The phase I reaction involves an oxidation, hydroxylation, reduction or hydrolysis reaction, which changes a functional molecular group on the drug. The phase II reaction consists of a conjugation of a glucuronate, glutathione, acetate or sulfate group to a functional group. When the functional group is changed the metabolite is rendered more water soluble so that it can be easily excreted. Most of the effects of diet on drug metabolism involve the phase I oxidation reaction.

The typical recommended diet for healthy Americans contains 50 to 60 percent of calories as carbohydrate and 0.8 g of protein per kg of body weight per day. High-carbohydrate and low-protein diets (60 percent of calories as carbohydrate, 0.6 g or less of protein per kg of body weight per day) decrease the metabolism of certain drugs such as theophylline. On the other hand, low-carbohydrate and high-protein diets (40 percent of calories as carbohydrate, 1.5 g of protein per kg of body weight per day) increase the levels of metabolizing enzymes, which increases the length of time it takes to achieve therapeutic levels of most drugs. Charcoal-broiled meats can also accelerate drug metabolism, as can the presence of indolic compounds in cruciferous vegetables such as broccoli, cabbage and brussels sprouts.

MAOIs and Tyramine

Many fermented foods, such as wine and aged cheese, contained tyramine. With monoamine oxidase inhibitors (MAOIs), tyramine triggers the release of norepinephrine from sympathetic nerve endings and release of epinephrine from the adrenal glands, resulting in a hypertensive reaction. If taken insufficient amounts, these foods may cause a hypertensive crisis in patients receiving MAOIs.

MAOIs include antidepressants such as tranylcypromine (Parnate), phenelzine (Nardil) and isocarboxazid (Marplan), antineoplastic agents such as procarbazine (Matulane), and antihypertensive agents such as pargyline (Eutonyl). Patients taking these agents should follow a tyramine-restricted diet. In general, any foods that are aged, fermented, overripe, leftover or spoiled should be avoided. Patients should be encouraged to consume fresh foods. Alcohol, caffeine and chocolate can act like tyramine and should be consumed only in moderation. The dietary restrictions should be maintained for two weeks following discontinuation of the agent.

Drug Antagonists

Natural licorice or licorice extracts containing glycyrrhizic acid can complicate hypertension and digitalis therapy by causing sodium retention and potassium excretion, leading to weight gain and hypokalemia. Most domestic licorice is made with a synthetic licorice flavor and therefore poses no problem.

The oral anticoagulant warfarin (Coumadin, Panwarfin) and vitamin K are antagonists of each other. Prothrombin time can be decreased if patients consume excessive amounts of foods rich in vitamin K, such as green leafy vegetables. Patients should avoid drastic dietary alterations while receiving warfarin.

Patients taking levodopa for the treatment of Parkinson's disease need to restrict their intake of pyridoxine to less than 5 mg per day. Pyridoxine is found in greatest amounts in meat, fish and poultry. Pyridoxine is a cofactor in the peripheral decarboxylation of levodopa to dopamine. Dopamine cannot cross the blood-brain barrier, and under these circumstances, symptoms of parkinsonism may be exacerbated. Carbidopa, an inhibitor of decarboxylase, does not cross the blood-brain barrier. It allows levodopa to enter the central nervous system before being metabolized in the periphery. The use of Sinemet, a compound that contains levodopa and carbidopa, does not require pyridoxine restriction.

Alteration of Urinary pH

Excessive consumption of alkaline ash beverages such as acidic fruit juices (orange juice, tomato juice and grapefruit juice), which are metabolized to an alkaline residue, will increase urinary pH, leading to an increased proportion of nonionized basic drugs and reabsorption, which may increase the potential for toxicity. Drugs such as quinidine and amphetamine are particularly susceptible to this effect since they are weak bases.

Drug-Alcohol Incompatibilities

The use of alcohol with drugs can result in clinically significant interactions. Interactions are more common in alcoholics than in persons who consume small amounts of alcohol.

Drug metabolism is affected by both acute and chronic use of alcohol. Chronic use results in enzyme induction, which leads to increased metabolism and the need for increased doses of anticonvulsants, sedatives and isoniazid. As a result, many alcoholics exhibit tolerance to sedatives. Acute use of alcohol saturates metabolic enzymes and leads to decreased metabolism of drugs metabolized by hepatic enzymes. Death can result from the concomitant use of barbiturates or narcotics and alcohol.

Large amounts of alcohol over a short period of time (bingeing) or small amounts in an individual who seldom drinks lead to an additive or synergistic effect with central nervous system depressants. Patients should be warned of additive sedation when taking narcotics, sedatives, antihistamines, tranquilizers, antidepressants, antipsychotics, anticholinergics, muscle relaxants or any drug with sedative action.

One of the best known interactions of drugs with alcohol is the disulfiram-like reaction. Drugs that inhibit the enzyme acetaldehyde dehydrogenase, which oxidizes acetaldehyde, lead to an accumulation of acetaldehyde and the associated nausea and vomiting within minutes of alcohol ingestion. The possibility of this reaction should be explained to patients taking metronidazole, chlorpropamide (Diabinese), disulfiram (Antabuse), MAOIs, chloral hydrate and certain cephalosporins (cefamandole (Mandol), cefoperazone (Cefobid), moxalactam (Moxam) and cefotetan (Cefotan)). Patients should also be cautioned about the use of over-the-counter cold preparations, which may contain up to 35 percent alcohol (70 proof).

The use of alcohol with aspirin, corticosteroids or NSAIDs can produce excessive gastrointestinal bleeding or gastritis, especially when these drugs are taken on an empty stomach. The ulcerogenic effect of these agents can be reduced by taking these drugs with food.

Alcohol produces generalized vasodilation except in the cerebral and coronary vasculature. To avoid transient postural hypotension, patients taking nitroglycerin should not drink alcohol within 30 minutes of nitroglycerine administration.

Patients receiving oral hypoglycemics may need to avoid alcohol because acute alcohol ingestion can alter carbohydrate metabolism, leading to hypoglycemia. Chronic alcohol use can cause increased hepatic metabolism of sulfonylureas, leading to hyperglycemia.