Handbook of
FOOD-DRUG INTERACTIONS

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life, health, and well-being." A 1992 survey lists the ten most common conditions treated with OTC products, which are headache, athlete's foot, the common cold, chronic dandruff, upset stomach, lip problems, premenstrual symptoms, menstrual symptoms, dry skin, and sinus problems. Six of these conditions rely primarily on orally ingested drugs for self-treatment.[1,3,4,5]

Prescription medications are being switched to OTC status with increasing frequency. More than 600 OTC products have ingredients or dosages previously available by prescription only. The U.S. Food and Drug Administration (FDA) has a division that reviews proposed OTC drugs. Drug approval for OTC use requires that the drug be on the market long enough to establish it to have "an acceptable safety margin, a low potential for misuse and abuse, the ability for the average consumer to self-diagnose, self-recognize, and self-treat the condition, and a label adequate to be understood by the lay consumer." Benefits of having OTC availability include decreased costs and enhanced patient autonomy; however, the potential risks of self-diagnosis may include inappropriate use, unnecessary use, or delay in treatment that could lead to increased costs and morbidity.[6]

Healthcare professionals need to be cognizant of drug–nutrient interactions in order to educate patients who self-medicate with OTC products. A nutrient is defined as a chemical substance needed for growth and maintenance of normal cells in both plants and animals. It should be understood that diet and nutrition can affect therapeutic response and these interactions have varying degrees of clinical significance. The interaction in some cases may be advantageous when it lessens side effects or increases therapeutic efficacy. On the other hand, drug–nutrient interactions can result in therapeutic failure. Testing for drug–nutrient interactions is still relatively new and has been reviewed in only a small percentage of drugs—the majority being prescription medications. As a result, health professionals often must make educated guesses about the effects of food on drug therapy.[7–11]

EFFECT OF FOOD/NUTRIENTS ON MEDICATION ABSORPTION

Food intake in relation to drug administration can have a significant impact on drug dissolution and absorption. The presence of food changes gastric motility, changes the gastrointestinal pH, and provides substances for drug and nutrient chelation and adsorption. Typically, when food is present in the stomach, drugs are absorbed more slowly; however, a clear distinction must be made between decreased rate of absorption and decreased amount of drug absorbed. A decreased absorption rate allows for increased nutrient interactions and possible delays in therapeutic efficacy without changing the overall bioavailability of the drug.[12–15]

The interaction of aspirin with food is an example of a nutrient delaying onset of activity without altering bioavailability. A study in 25 subjects found that food roughly halved the serum salicylate level 10 and 20 min after a 650-mg dose when compared with placebo. Additional studies have confirmed this finding. It is likely that the aspirin is adsorbed onto the food and the food itself delays gastric emptying. Food intake markedly slows the absorption of aspirin and thus the time to onset of therapeutic effect. On the other hand, a delay in absorption may be beneficial.

Cimetidine is given with food to assist in maintaining a therapeutic blood concentration. A fraction of cimetidine is absorbed while food is present, allowing the remaining drug to be dissolved once the gut is cleared. Thus, therapeutic levels are maintained throughout the dosing interval.[13,16–18]

Although it is frequently assumed that food reduces drug absorption, lipophilic drugs are, in many cases, more readily used when taken with a high-fat meal. The increased residency in the gut improves drug dissolution. Water-insoluble drugs (such as the prescription drugs spironolactone and griseofulvin) are better absorbed when taken directly after a meal. Owing to their lipophilic nature, supplements for vitamins A, E, D, and K have enhanced absorption when taken with a high-fat meal.[19,20]

Chelation is an additional factor that influences drug absorption. Chelation involves the formation of a complex between certain dietary components, especially divalent or trivalent cations (e.g., Ca, Mg, Al, Fe, and Zn) and certain drugs. The complex is a less soluble substance; therefore, absorption of the nutrient and drug is decreased. Antacids containing aluminum, magnesium, and calcium or foods rich in copper, calcium, magnesium, zinc, and iron are most often responsible for chelation. To prevent chelation, antacids should be dosed 2–3 h apart from foods containing these nutrients. Tannins, a component of strong tea, coffee, and some wines, form complexes with iron and other heavy metals, which are then not absorbed. It may be prudent to avoid taking iron supplements at the same time as these liquids.

Specific nutrients and food components also influence the rate of drug absorption. A high-carbohydrate meal slows the absorption of many drugs. Fiber and calcium can bind with a drug to prevent absorption. The absorption of acetaminophen is slowed by the presence of pectin, a fiber. Acidic juices and cola may cause rapid dissolution of some drugs. A drug with its primary activity in the intestines may be broken down too early if administered with an acidic beverage. Thus, the drug's efficacy is greatly reduced. In contrast, juice with a high vitamin C content enhances the absorption of iron supplements.[21,22]

EFFECT OF FOOD/NUTRIENTS ON MEDICATION METABOLISM

The metabolism of many substances including drugs occurs primarily through the mixed-function oxidase system and the conjugating system of the cell cytosol. The mixed-function oxidase system catalyzes oxidative reactions (phase I) of a number of drug classes as well as endogenous substance, fatty acids, and prostaglandins. More than 30 isoenzymes of the system have been identified as belonging to the cytochrome P_{450} series (CYP_{450}). The major enzymes responsible for drug metabolism are CYP3A4, CYP2D6, CYP1A2, and the CYP2C. In the conjugating system, drugs are primarily converted to glucoronides, ester sulfates, or glutathione conjugates (phase II). Phase I and II reactions occur in the liver as well as in the intestinal mucosa.[23,24]

Dietary components of food may alter this hepatic metabolism by induction or inhibition of the mixed-function oxidase system. Induction of the enzyme system results in an increased metabolism of a parent drug to metabolites and thus a decrease

in the availability of the parent drug. As a result, enzyme induction commonly produces lower blood levels of the parent drug. Lower blood levels may result in decreased efficacy of the drug. If the parent drug, however, must be converted by the enzyme system to an active metabolite, induction may be associated with increased toxicity due to higher concentrations of the metabolite. High-protein, low-carbohydrate diets induce the mixed-function oxidase system and promote metabolism of drugs that are substrates of this system. Indoles found in cruciferous vegetables, such as cabbage and Brussels sprouts, and chemicals in charcoal-broiled meats significantly induce chemical oxidations of medications as well. Smoked and preserved meats likely also contain chemicals oxidized by CYP_{450} isoenzymes.[22,23]

On the other hand, bioflavanoids and other substances found naturally in fruits and vegetables may inhibit drug hepatic metabolism. Inhibition of the mixed-function oxidase system typically results in elevated serum levels of the parent drug, prolonged therapeutic efficacy, and increased incidence of adverse effects. Several components of grapefruit juice and whole grapefruit are assumed to be responsible for inhibition of the CYP_{450} isoenzymes 1A2 and 3A4. An appreciable increase of systemic availability of certain medications can occur when administered with grapefruit juice. Acetaminophen and naproxen are substrates of these isoenzymes; therefore, grapefruit juice may theoretically increase drug levels. In contrast, charbroiled food is an inducer of 1A2 and 3A4 and may decrease the efficacy of acetaminophen and naproxen. Minimal clinical significance, however, has been found with interactions between OTC products and grapefruit juice.[23,24]

Nutrients have also been shown to influence hepatic blood flow. Any drug absorbed in the intestine is taken directly to the liver. The enterohepatic circulation is a fundamental process in all pharmacokinetic processes involving orally ingested drugs. A number of drugs undergo biotransformation during this first pass through the gut wall and liver, with its complex enzyme systems. These biotransformations occur prior to drug transportation into circulation. Protein may increase the rate of blood flow to the liver and, therefore, increase the metabolism of a drug. Increased metabolism, as with induction of the mixed-function oxidase system, leads to changes in the amount of parent drug available. Blood levels, efficacy, and side effects of a drug may be increased or decreased as a result.[3,5,14,22] (See Table 12.1.)

EFFECT OF FOOD/NUTRIENTS ON MEDICATION EXCRETION

Food and nutrients may alter the renal excretion of some drugs. At high urinary pH values, weakly acidic drugs largely exist as ionized lipid-soluble molecules that cannot diffuse back across the renal tubule into blood and are lost in the urine. The converse is true for weak bases. Salicylic acid offers a useful example applicable to drugs likely to be affected by diet-related increases in urinary pH. Alkaline urine causes the salicylic acid to be reabsorbed from the urine. Drugs excreted from acidic urine but reabsorbed from alkaline urine include antihistamines, ascorbic acid, and nicotine. The clinical significance of this is usually small. Most drugs are transformed by the liver to inactive metabolites, and few are excreted unchanged in the urine.[3,7,25]

Table 12.1 Nutrient Effects on Drugs

Nutrients Involved	Drug Affected	Effect on Drug	Recommendation
Starches, clay, egg yolks	Iron	Decreased absorption	
Coadministration of food	Riboflavin	Increased absorption	
Coadministration of food	Thiamine	Delayed absorption	
Coadministration with pectin (fiber)	Acetaminophen	Delayed absorption and onset	
Coadministration of food	Cimetidine	Delayed absorption and onset	
Coadministration of food	Aspirin	Delayed absorption and onset	
Coadministration of food	Pseudoephedrine	Delayed absorption and onset	
Coadministration of food	Ibuprofen, ketoprofen, naproxen	Food delays absorption and onset but not significant; may cause GI upset, bleeding, ulceration or perforation	Administer with food to decrease GI upset
Coadministration of food	Famotidine	Slightly increased absorption	
Coadministration of food	Potassium	Delayed absorption and onset	

EFFECT OF MEDICATION ON FOOD/NUTRIENT ABSORPTION

Alterations in gastric pH due to drugs, such as antacids and H_2 antagonists, may influence the absorption of other drugs and nutrients. Prolonged use of antiulcer drugs, such as omeprazole, lansoprazole, pantoprazole, famotidine, ranitidine, nizatidine, or cimetidine, may decrease the absorption of vitamin B_{12}, thiamin, and iron. Drugs that change the pH in the different regions of the intestines may also influence nutrient absorption. Potassium chloride found in salt substitutes lowers the pH in the ileum, impairing vitamin B_{12} absorption. Antacids can produce an increase in gastric pH to alkaline levels (i.e., >7.2). The absorption of calcium, iron, magnesium, zinc, and folacin decreases in such an environment. Calcium carbonate given in 500-mg or greater doses increases the rate of absorption of folic acid due to an increased dissolution rate. Aluminum in aluminum hydroxide antacids can combine with phosphorus to form an insoluble complex that is excreted in the feces, with decreased phosphate absorption and blood levels. This interaction may be valuable in the treatment of hyperphosphatemia but harmful in the face of symptomatic hypophosphatemia. Aluminum antacids can also precipitate bile acids, leading to decreased absorption of vitamin A. Bisacodyl, a stimulant laxative, should not be taken with milk. The dissolution of this enteric-coated tablet is pH dependent. The milk may cause the drug to dissolve in the stomach, rather than in the small intestine, resulting in severe abdominal cramping and gastrointestinal irritation.[14,22]

Many OTC products interfere with gastric motility and thus the absorption of nutrients. Antacids and anticholinergic drugs affect bowel motility and thus the rate at which the nutrient moves through the gastrointestinal tract. Aluminum antacids may relax the gastric smooth muscle and cause a delay in gastric emptying. Anticholinergic drugs, such as antihistamines, slow peristalsis, thus slowing gastric emptying. The decreased transit time may result in more nutrient–drug interactions and a slow therapeutic response. On the other hand, laxatives may stimulate peristalsis, causing nutrients to be moved through the gut more quickly. Prolonged use of stimulant laxatives (e.g., bisacodyl) or saline laxatives (e.g., milk of magnesia) may decrease absorption of electrolytes such as calcium and potassium.[1,2,26]

Mineral oil acts as a physical barrier to the absorption of fat-soluble vitamins A, D, E, and K, as well as beta carotene and phosphorus. Mineral oil used as a laxative coats the lining of the small intestines. The body does not absorb it. Many nutrients, particularly fat-soluble vitamins, are dissolved in the mineral oil and are never absorbed. A variety of metabolic abnormalities such as low serum calcium and phosphate may result due to decreased vitamin D absorption. Mineral oil is rarely used, particularly in elderly patients, due to the risk of lipid pneumonitis from aspiration of oil droplets.[1,7]

Drugs may also directly affect nutrient absorption by damaging the mucosal wall of the small intestines, thus preventing a drug from being absorbed. Aspirin is a typical example of a drug that induces mucosal damage in the gut. Aspirin and other nonsteroidal products cause direct gastric irritation by breaking the gastric mucosal barrier. They also block the prostaglandins that produce gastric mucosal secretions to protect the stomach. As a result, blood is lost through the gastrointestinal tract. This gastrointestinal mucosal damage alters the absorption of iron and calcium. Chronic salicylate ingestion is a common cause of iron deficiency anemia.[4,13,15,18,19]

EFFECT OF MEDICATION ON FOOD/NUTRIENT METABOLISM

Cimetidine, an H_2 antagonist, inhibits the activity of cytochrome P_{450}, thereby slowing the metabolism of many substances that are substrates of the mixed-function oxidase system. Ranitidine has a lesser affinity to CYP_{450} than cimetidine. Therefore, clinically significant drug interactions are less likely to occur when ranitidine is chosen in place of cimetidine. Nizatidine and famotidine represent other H_2 antagonists that do not appear to produce interactions via this mechanism. Thus, it is reasonable to anticipate that the action of agents metabolized via this pathway would remain at normal levels or increase. The potential exists for nutrients metabolized via the liver to reach increased levels due to cimetidine-induced inhibition. No interactions between them have been documented at this time. Cimetidine may have an additional role in drug–nutrient interactions. Cimetidine (but not the other H_2 antagonists) decreases hepatic blood flow and thereby increases the bioavailability of nutrients or other drugs.[22,23,24]

Although not currently documented with OTC products, drugs may increase the metabolism of certain nutrients, resulting in higher dietary requirements. Anticonvulsants, phenobarbital, and phenytoin increase the metabolism of folic acid and