Drug–Food Interactions in Clinical Practice

Weeranuj Yamreudeewong, PharmD; Neil E. Henann, PharmD; Anthony Fazio, PharmD;
Dennis L. Lower, MD; and Thomas G. Cassidy, MD
Cheyenne, Wyoming; Monroe, Louisiana; and Livingston, New Jersey

Drug–food interactions are a significant problem in clinical practice. Foods may alter the effects of drugs by interfering with pharmacokinetic processes, such as absorption and elimination. For example, absorption of tetracyclines is decreased when taken with milk or other dairy products. Pharmacologic and pharmacodynamic mechanisms also play an important role in drug–food interactions by altering drug effects. An example is the interaction of warfarin sodium with leafy green vegetables, whereby the hypoprothrombinemic effect of warfarin may be decreased and thromboembolic complications may develop. Similarly, certain drugs may have an effect on food intake, absorption, metabolism, and utilization. Numerous drugs, such as antineoplastic agents, have been shown to suppress appetite, resulting in decreased food intake and nutritional deficiency.

It is important that health care providers, such as physicians, pharmacists, and dietitians, recognize and work as a team to prevent significant drug–food interactions. Minimizing adverse drug–food interactions would improve patient care by optimizing therapeutic effects and maintaining proper nutritional status.

Key words. Food–drug interactions; drugs; food; pharmacology; drug toxicity; therapeutic failure; nutritional deficiency. (*J Fam Pract* 1995; 40:376-384)

As with drug–drug interactions, drug–food interactions represent a substantial clinical problem that may result in adverse drug effects or toxicity. In some cases, the interacting effects may cause therapeutic failure[1] or nutritional deficiency.[2] Recent guidelines of the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) have encouraged hospital pharmacists and dietitians to monitor interactions between drugs and foods in patients.[3] This article reviews and updates the database for clinicians regarding drug–food interactions, focusing on those of clinical significance.

Mechanisms of Drug–Food Interactions

The interactions of foods with drugs can be classified in two major categories: pharmacokinetic and pharmacodynamic interactions.

Pharmacokinetics

The absorption, distribution, metabolism, and excretion of a drug is known as *pharmacokinetics*.[4] Foods may affect the rate or extent, or both, of drug absorption by altering gastric pH, secretion, and gastrointestinal motility and transit time. Alterations in the *rate* of a drug's absorption caused by the ingestion of certain foods generally is not considered as clinically important as changes in the *extent* of its absorption. However, a delay in time to peak plasma concentration or time to achieve steady-state therapeutic concentrations may occur if the rate of absorption is decreased. The types of food and the amount or size of a meal also can affect the absorption of a drug. Certain constituents in foods may chelate or adsorb the drug, resulting in a decrease in the extent and rate of its absorption.[5]

ISSN 0094-3509

Food may interact with a drug by interfering with its metabolism. For example, charcoal-broiled meat can activate hepatic microsomal enzymes, causing an increase in theophylline metabolism or clearance.[6] Likewise, certain drugs may interfere with the metabolism of food or food additives, as in the case of metronidazole and alcohol.[7]

Pharmacodynamics

The study of drug effects is known as *pharmacodynamics*. Foods may interact with drugs by influencing their effects or pharmacologic actions, as in the case of diets high in vitamin K, which decrease the effects of warfarin sodium,[8–11] or alcoholic beverages, which increase the depressant effects of benzodiazepines on the central nervous system.[12] Foods may interfere with drugs by simply potentiating the effect of the drug, such as the additive effect of caffeine on theophylline.[13]

Effect of Foods on Specific Drug Therapy

Antimicrobial Agents

The absorption of several antimicrobial agents, such as tetracyclines and certain fluoroquinolones, may be decreased by chelation with dietary cations, such as calcium and magnesium in milk or other dairy products[5,14] (Table 1). Neuvonen and Kivisto,[15] however, found no important effects of milk or yogurt on the absorption of ofloxacin. It has also been reported that Osmolite, an enteral feeding preparation, does not significantly decrease the absorption of ciprofloxacin in healthy volunteers.[16] It is unknown whether the result of this drug–food interaction can be applied to critically ill patients.

Food or a regular meal has been shown to reduce the bioavailability of azithromycin.[17] Food also may significantly affect the absorption of other macrolide antimicrobial agents, such as erythromycin[18] (Table 1).

Metronidazole, administered systemically or applied intravaginally, has been reported to cause a disulfiram-like reaction when used concurrently with alcohol.[7,19] Other drugs, such as cephalosporins containing methyltetrazolethiol (MTT) side chain in their structures, also can interact with alcohol, causing a similar reaction.[20–22] These cephalosporins include moxalactam disodium, cefoperazone sodium, cefamandole nafate, cefotetan disodium, ceftriaxone sodium, and cefmetazole sodium. The mechanism of these drug–alcohol interactions may be related to the inhibition of aldehyde dehydrogenase and the sub-

sequent accumulation of acetaldehyde, resulting in facial flushing, tachycardia or palpitations, headache, nausea, and vomiting. Caution should be exercised when using these cephalosporins or metronidazole in hospitalized patients because of the potential alcohol content in co-administered medications.

Isoniazid may interfere with vitamin B_6 metabolism, which may lead to peripheral neuropathy unless the patient has adequate and proper nutritional intake or receives a vitamin B_6 supplement.[23,24] It has been indicated that isoniazid-induced neuropathy is dose-related and more common with doses of isoniazid >5 mg/kg.[25]

Food has also been shown to significantly decrease the absorption of didanosine and increase the absorption of griseofulvin[26,27] (Table 1).

Cardiovascular and Cholesterol-Lowering Drugs

Although food may decrease the rate of absorption of digoxin, the total extent of its absorption is not significantly altered. Steady-state serum digoxin concentrations also may be delayed when administered with food or immediately after a regular meal, and diets with high bran fiber may significantly reduce digoxin absorption, resulting in decreased serum concentrations and effectiveness.[28]

There are conflicting findings regarding the effect of food on captopril effectiveness. Food has been shown to decrease captopril bioavailability by more than 50% with a significant delay in hypotensive effect.[29] However, other randomized crossover studies did not find a significant decrease in captopril absorption and hypotensive effect when administered with food or after meals.[30,31] Therefore, further clinical studies are needed to determine the interaction between captopril and food.

Because of the hyperkalemic side effect associated with angiotensin-converting enzyme (ACE) inhibitors,[32] patients should be aware of the potential interaction between ACE inhibitors and salt substitutes containing potassium, especially when potassium supplements are being administered concurrently. ACE inhibitors have also been shown to cause an alteration in taste or a loss of the sense of taste, which may result in decreased food intake in the patient.[33] Alternative drugs may be required if this adverse effect occurs.

It has been reported that concentrated grapefruit juice causes a significant (an average of 280%) increase in serum felodipine concentrations, resulting in an enhanced effect of blood-pressure reduction.[34] Edgar et al[35] suggested that the inhibitory effect on felodipine metabolism by flavonoid compounds in grapefruit juice might be responsible for this drug–food interaction. Several investigators[36–38] found that foods high in fiber, such as oat

Table 1. Clinically Important Drug–Food Interactions

Oral Drug	Food	Mechanism	Recommendations/Comments
Antimicrobial agents			
Ampicillin	Regular meal	↓ absorption of ampicillin	Give the drug 1 h before or 2 h after meals; may use alternatives, such as amoxicillin
Cefuroxime axetil, cefpodoxime	Regular meal	↑ absorption of cefuroxime or cefpodoxime	Give the drug with food or meals
Ofloxacin	Regular meal	↓ absorption of ofloxacin	Give the drug 1 h before or 2 h after meals
Ciprofloxacin	Dairy products such as milk and yogurt	↓ absorption of ciprofloxacin	Give the drug 1 h before or 2 h after dairy products
Ciprofloxacin, ofloxacin	Enteral feedings	↓ absorption of either drug	Conflicting data exist regarding the effect of enteral feedings on the absorption of either drug; however, withholding the enteral feeding 2 h before and 2 h after either drug administration is advisable
Tetracyclines (except doxycycline and minocycline)	Regular meal or dairy products, such as milk	↓ absorption of tetracyclines	Give the drug 1 h before or 2 h after the dairy products, or use the formulations that are not affected by dairy products, such as doxycycline
Azithromycin	Regular meal	↓ absorption of azithromycin by 45% to 50%	Give the drug 1 h before or 2 h after meals, or, if possible, use other alternative, such as clarithromycin
Erythromycin stearate	Regular meal	↓ absorption of erythromycin stearate	Give the drug 1 h before or 2 h after meals, or use other erythromycin preparations that are not affected by food, such as enteric-coated erythromycin base
Erythromycin base	High-fat meal	↓ absorption of erythromycin base of 72%	Avoid giving with high-fat meals
Rifampin	Regular meal	↓ absorption of rifampin	Give the drug 1 h before or 2 h after meals
Griseofulvin	High-fat meal	↑ absorption of griseofulvin	Give the drug with meals, preferably with heavy meals such as lunch or dinner
Dideoxyinosine	Regular meal	↓ absorption of dideoxyinosine	Give the drug 1 h before or 2 h after meals, or use an alternative such as dideoxycytidine or zidovudine if possible
Atovaquone	High-fat meal	↑ absorption of atovaquone by ~ 3 fold	Same as for griseofulvin
Cardiovascular drugs			
Digoxin	Regular meal	Altered gastrointestinal transit time and motility, resulting in ↓ rate of absorption of digoxin	Give the drug ½ to 1 h before or 2 h after meals if possible, or monitor serum drug levels and clinical response closely
Digoxin	Bran fiber	↓ absorption of digoxin	Give the drug ½ to 1 h before or 4 h after bran fiber, monitoring serum drug levels and clinical response closely
Felodipine	Concentrated grapefruit juice (double-strength)	Possibly due to inhibition of metabolism of felodipine	Give the drug with other fluid, or, if applicable, use other calcium antagonists, such as amlodipine
Captopril	Regular meal	↓ absorption of captopril	Conflicting data exist; current suggestion is to give the drug 1 h before or 2 h after meals, or, if possible, use other alternative, such as enalapril

Table 1. *Continued*

Oral Drug	Food	Mechanism	Recommendations/Comments
Angiotensin-converting enzyme (ACE) inhibitors	Foods with high salt substitute (potassium-containing)	Potentiation of the ↑ of serum potassium	Cardiac arrhythmias may occur; avoid use of salt substitute
Potassium-sparing diuretics	Salt substitute in foods	Potentiation of the ↑ of serum potassium	Cardiac arrhythmias may occur; avoid use of salt substitute
Warfarin	Foods with high vitamin K (cauliflower, beans, spinach, broccoli, cabbage, turnip greens, lettuce, kale, fish, etc)	↓ the availability of vitamin K for activation of vitamin K–dependent clotting factors	Foods with high level of vitamin K should be consumed in moderate amounts
Warfarin	Enteral feedings	↓ absorption of warfarin	Withholding the enteral feeding 3 h before and 3 h after the drug administration is advisable
Theophylline	High carbohydrate and low protein diets	May ↓ hepatic clearance of theophylline	Monitor serum drug levels and clinical response is advisable
Theophylline	Low carbohydrate and high protein diets or charcoal-broiled beef	May ↑ hepatic clearance of theophylline by 30%	Monitoring serum drug levels and clinical response is advisable
Theophylline-timed release (24 h)	Regular meal	Interference of the design of formulation	Monitor serum drug levels and clinical response, or use other sustained-release theophylline formulation, such as Theodur; dosing regimen should be set appropriately
Theophylline	High-fat meal	↑ Absorption theophylline	Monitor serum drug levels clinical response, or do not administer with high-fat meals
Phenytoin	Enteral feeding preparations	↓ absorption of phenytoin	Withhold the enteral feeding 2 h before and 2 h after phenytoin administration; monitor serum drug levels and clinical response
Antiparkinson drugs			
Levodopa (including levodopa/carbidopa)	High-protein diet	Competition with drug absorption and CNS transport by amino acids	Monitor clinical response and avoid high-protein diet if appropriate
Monoamine oxidase (MAO) inhibitors†	Tyramine-rich foods	↑ catecholamine levels by inhibiting their degradation and also ↑ amount of tyramine absorbed	Avoid foods with high content of tyramine (strongly suggested); monitor patient's clinical status

*ACE inhibitor: *benazepril, captopril, enalapril, fosinopril, lisinopril, quinapril,* and *ramipril.*
†MAO inhibitor *antidepressants:* isocarboxazid, phenelzine, tranylcypromine; *and antineoplastic:* procarbazine.

bran, oatmeal, and soluble-fiber cereal, decrease the absorption of lovastatin, resulting in a substantially high level of low-density lipoprotein cholesterol. Additional studies may be required to clearly define the potential drug–food interactions of lovastatin and other agents in this drug group (HMG-CoA reductase inhibitors).

Oral Anticoagulant

Foods that are high in vitamin K, such as leafy green vegetables and beef liver, may counteract the effects of oral anticoagulants, such as warfarin (Table 1). It has been indicated that foods rich in vitamin K may cause a significant warfarin-resistant effect, thereby resulting in a low prothrombin time, which may ultimately lead to clot formation or thrombosis.[8,9] Several investigators have also found that enteral feeding products containing vitamin K interact with warfarin, resulting in a decrease of its hypoprothrombinemic effect.[39,40] Although most enteral feeding preparations have been reformulated with lower contents of vitamin K, warfarin absorption may be impaired as a result of physical or chemical interactions with

other ingredients contained in newly formulated enteral feeding preparations.[41]

Blickstein et al[42] reported a significant decrease of INR (international normalized ratio) values (compared with adequate anticoagulation values) in two patients following the ingestion of avocado. They also found a return of INR to the therapeutic range when avocado was eliminated from the patients' diets. It has been suggested that the high fat content of avocado reduced the absorption and thus decreased the effectiveness of warfarin.

Bronchodilators

Theophylline, a xanthine derivative, undergoes extensive hepatic metabolism. The effect of food on theophylline pharmacokinetics depends on the preparation or formulation of theophylline. Additionally, the type or composition of foods can alter theophylline disposition, thus causing an increase or decrease in serum drug levels.

It has been reported that high-protein low-carbohydrate diets or high-carbohydrate low-protein diets may alter hepatic clearance of theophylline[43,44] (Table 1). However, the most significant clinical interaction of food and theophylline occurs with specific sustained-release theophylline preparations (Table 1). Food may induce a sudden release (dose-dumping) of once-daily dosing preparations of theophylline, resulting in an increase in serum drug levels and ultimately toxicity.[45]

Jonkman and colleagues[46] also reported that caffeine (a methylxanthine derivative) increased serum theophylline concentrations by 20% to 30% and the half-life by 3 hours (from 6.3 to 9.3 hours). Sato et al[13] also indicated that dietary caffeine significantly decreased clearance and increased the half-life of theophylline ($P<.05$). These investigators suggested that caffeine may inhibit the hepatic metabolism of theophylline, resulting in decreased clearance and increased serum drug levels. Caffeine also has some bronchodilatory effects that may further enhance the pharmacologic effects of theophylline. A lower dosage of theophylline may be desirable in patients who consume excessive amounts of coffee (more than six cups daily).

Anticonvulsants

Enteral feeding preparations have been shown to significantly reduce serum phenytoin levels, especially when continuously administered concomitantly with oral phenytoin (Table 1). The mechanism of these drug–food interactions may be related to decreased absorption by protein caseinates or calcium in the enteral feedings.[47–49] The enteral feedings may need to be withheld for a few hours before and after phenytoin administration (Table 1).[50] If continuous administration of enteral feedings is required, phenytoin may be administered intravenously. Oral suspension of phenytoin should be diluted before it is administered through a nasogastric tube, and tubing should be flushed after the administration. The patient's clinical response, especially seizure control, and the serum phenytoin concentrations should be closely monitored. Dietary puddings, which have a similar constitution to that of enteral feedings, also may decrease phenytoin absorption.[51]

Applesauce has been reported to significantly increase serum phenytoin concentrations (concentrations increased from 11.22 ± 3.52 $\mu g/mL$ to 21.09 ± 8.90 $\mu g/mL$ in eight patients, $P<.05$).[51] The exact mechanism of this food–drug interaction is unclear, but the higher serum phenytoin concentrations may be caused by increased absorption.

It has been shown that food has no effect on felbamate tablet absorption; however, the effect of food on absorption of felbamate suspension has not been evaluated. Recently, neural tube defect, an adverse consequence in neonates born to women receiving valproic acid as an anticonvulsant during pregnancy, has gained the attention of health care professionals and the public. The mechanism of valproic acid–induced neural tube defect is unknown; however, a reduction in serum folate levels has been suggested as a potential cause.[52]

Other anticonvulsants, such as carbamazepine, phenobarbital, and primidone, also have been shown to cause neural tube defect. It has been strongly suggested that pregnant women, especially those receiving anticonvulsants, should receive folic acid supplements and consume foods rich in folic acid or folate (such as leafy green vegetables, liver, and meats) before and throughout the prenatal period.[53] However, caution is warranted when supplemental folic acid is concurrently used with phenytoin. The potential interaction between phenytoin and folic acid can result in decreased serum phenytoin levels and, thus, decreased seizure-control.[54] If seizures cannot be controlled by phenytoin, other anticonvulsants may be used.

Protracted use of high dosages of phenytoin may interfere with dietary folic acid absorption resulting in megaloblastic anemia.[55] The use of phenytoin and phenobarbital has been reported to cause derangements of vitamin D metabolism, resulting in osteoporosis, especially in institutionalized patients and the elderly.[56]

Antiparkinson Drugs

The absorption of levodopa may be delayed in patients on high-protein diets.[57–59] The resulting decrease in serum

Table 2. Interactions between Foods Containing Tyramine and Monoamine Oxidase Inhibitors

Foods Containing Tyramine	Example	Remarks
High content: not allowed to consume		
Matured, aged cheeses	Boursault, Camembert, cheddar, Emmenthaler, Stilton, bleu	Most cause reactions
Aged/fermented or smoked or pickled meats, poultry, fish	Beef-liver or chicken pâté, fermented sausages (bologna, pepperoni, salami, summer sausage), corned beef, fish (pickled herring), and shrimp paste	Fermented sausages contain high levels of tyramine. Meat and fish: safe if fresh. Shrimp paste contains significantly high amount of tyramine
Bean curd	Soy bean paste and miso soup	Reactions reported with miso soup
Red wines	Sherry, vermouth, Chianti, burgundy, and champagne	Reactions reported with Chianti, champagne, and other wines
Yeast extracts	Brewer's yeast, Marmite	Yeast used in baked products is usually safe
Moderate content: small or limited amount may be allowed		
Overripe avocado		
Pale and pasteurized beers		
Meat extracts	Consommé, bouillon	Considered safe if fresh
Soy sauces	Teriyaki	Reactions have been reported
Protein-extract soups	Soups made by liquid or powdered protein	Should be avoided if possible
Low content: allow to consume		
Sour cream, yogurt, milk		Appear to be safe
Mozzarella and American cheeses	Cream cheese, cottage cheese	Unfermented cheese may be safe
Fruit	Raisins, grapes, figs, oranges, pineapple, and bananas	Large amount of bananas can cause reactions, peel from bananas has tyramine levels, overripe figs should be avoided
Distilled spirits, wines (in moderate amount)	Scotch, vodka, rye, and gin	
Beer and ale		Domestic brands contain much lower level of tyramine; nonalcoholic beers may contain tyramine

NOTE: *Data on table are derived from* Medical Letter on Drugs and Therapeutics,[62] *and* Murphy.[63]

levodopa concentrations may cause an "on and off" phenomenon, a worsening of parkinsonian symptoms (Table 1).

Selegiline hydrochloride, a monoamine oxidase (MAO)–B inhibitor, has not been shown to significantly interact with foods containing tyramine, as do MAO-A inhibitors. Therefore, patients taking selegiline may not require dietary restrictions. However, Brown[60] and Schulz[61] and their co-workers suggested caution regarding the possible interaction between tyramine-rich foods and a daily dose of >20 mg selegiline (usual recommended daily dose: 10 mg).

Antidepressants

Although interactions between MAO-A inhibitors and tyramine-rich foods are uncommon, patients receiving MAO inhibitors should be aware of this potentially dangerous drug–food interaction[62,63] (Tables 1 and 2).

Liu and Rustgi[64] reported a case of hypertensive crisis (blood pressure, 200/100 mm Hg) and severe chest pain associated with tranylcypromine sulfate (an MAO inhibitor) therapy after ingesting a meal containing cheese. Aged or ripened cheeses contain far higher amounts of tyramine than do non-aged cheeses. Non-aged cheeses,

such as cream cheese or cottage cheese, have not been shown to cause significant interactions with MAO inhibitors.[65]

Lithium

High- and low-salt diets may increase and decrease the renal excretion of lithium, respectively,[66] causing changes in lithium therapeutic response. It has been suggested that this drug–food interaction relates to how the kidney excretes and reabsorbs these ions. This drug–food interaction may be more important when diuretics, such as hydrochlorothiazide, are coadministered.

Patients on a low-salt diet, as recommended for hypertension or congestive heart failure, may be susceptible to this food–drug interaction. The elderly, who generally have decreased food intake, also may be vulnerable to this interaction. The increased reabsorption of lithium that occurs with low-salt diets or low serum sodium may cause an increase in serum lithium concentrations, and possibly lithium toxicity, which can cause nausea, vomiting, diarrhea, arrhythmias, and seizures.

Laxatives

Prolonged use of laxatives, especially stimulant laxatives (eg, bisacodyl) or saline laxatives (eg, milk of magnesia), may decrease the absorption of electrolytes, eg, potassium, calcium, and magnesium in foods.[67]

Stimulant laxatives, such as oral bisacodyl, should not be taken with milk because they are an enteric-coated formulation, the dissolution of which is pH-dependent. Taken with milk, oral bisacodyl may dissolve in the stomach rather than in the small intestine, causing gastric irritation and abdominal cramps and preventing the desired laxative effect.[68]

In addition, prolonged use of large doses of mineral oil may result in reduced absorption of fat soluble vitamins A, D, E, K, and beta-carotene in foods.[69] Decreased absorption of these fat-soluble vitamins may lead to a variety of metabolic abnormalities, such as low serum calcium and phosphate levels resulting from a decrease in vitamin D absorption.

Miscellaneous

Bile acid sequestrants, such as cholestyramine or colestipol, may decrease absorption of vitamins A, D, E, and K in foods by interfering with the activity of bile acid,[70] which is an important emulsifying agent for the absorption process of fat soluble vitamins.

The prolonged use of antacids containing aluminum ions may decrease the absorption of phosphate from foods owing to the binding of aluminum and phosphate ions, resulting in hypophosphatemia.[71]

Fluoxetine hydrochloride, a selective serotonin-reuptake inhibitor antidepressant, has been shown to suppress appetite, which may result in weight loss.[72,73] Several antineoplastic drugs reportedly suppress appetite or cause mucositis, which may affect the patient's oral intake, resulting in nutritional deficiency. Several useful references on this potential complication are available.[74,75]

Alcohol (ethanol) is an additive to many foods and beverages. Alcohol in foods or beverages may interact with certain drugs, such as sulfonylureas (especially chlorpropamide[76]) and certain antimicrobial agents[7,22] (eg, metronidazole and several cephalosporins), resulting in a disulfiram-like reaction. Alcohol also can potentiate the hypoglycemic effect of sulfonylureas and insulin by suppressing gluconeogenesis, which can result in a reduction of blood glucose.[77] Because of the depressant effects of alcohol on the central nervous system (CNS), additive effects of alcohol and CNS-depressant drugs, such as benzodiazepines, phenothiazines, and tricyclic antidepressants, may occur.[78–80]

In general, occasional ingestion of large amounts of alcohol may cause enzyme inhibitory effects on certain drugs that are primarily metabolized by the liver. However, long-term use of alcohol may cause hepatic enzyme induction, significantly affecting the metabolism of certain drugs. A more comprehensive review regarding these interactions is available elsewhere.[81,82]

Conclusions

Although interactions between foods and drugs are not as great a concern as interactions between certain drugs, some foods substantially affect drug therapy, resulting in harmful reactions. Ingesting foods high in vitamin K during warfarin therapy, for example, can decrease the anticoagulant effect of warfarin and increase the potential for thromboembolic events or even death.

In some cases, drug substitution may be beneficial. For patients who prefer to take oral medications with milk, for instance, the suppository preparation of bisacodyl can be substituted for the oral medication.

Patient counseling by pharmacists along with the use of special colored labels or printed instructions would be useful to decrease the potential of drug–food interactions. The decision regarding these special labels is based on widely accepted, standard references such as *The United States Pharmacopeia Drug Information*,[83] *Drug Facts and Comparisons*,[84] and *CCIS (R) System*[85] (a computerized drug information program, Micromedex, Inc, Engle-

wood, Colo). Some special labels designed for patient education, such as those used to warn consumers of potential interactions between iron or tetracycline and milk products, are currently in use.

Whenever well-documented data regarding specific drug–food interactions are not available, clinical judgment and close monitoring are essential. The information presented in this review is intended to help physicians, pharmacists, and dietitians guard against significant food–drug interactions, with the goal of ultimately improving patient care by minimizing adverse interactions, optimizing the effectiveness of drug therapy, and maintaining proper nutritional status.

References

1. Trovato A, Nuhlicek DN, Midtling JE. Drug–nutrient interactions. Am Fam Physician 1991; 44:1651–8.
2. Hathcock JN. Nutrient–drug interactions. Clin Geriatr Med 1987; 3:297–307.
3. Murray JJ, Healy MD. Drug–mineral interactions: a new responsibility for the hospital dietitian. J Am Diet Assoc 1991; 91:66–70, 73.
4. Riegelman S, Rowland M. Effect of route of administration on drug disposition. J Pharmacokinet Biopharm 1973; 1:419–34.
5. Leyden JJ. Absorption of minocycline hydrochloride and tetracycline hydrochloride: effect of food, milk, and iron. J Am Acad Dermatol 1985; 12:308–12.
6. Anderson KE, Conney AH, Kappas A. Nutrition and oxidative drug metabolism: relative influence of dietary lipids, carbohydrate and protein. Clin Pharmacol Ther 1979; 26:493–501.
7. Tunguy-Desmarais GP. Interaction between alcohol and metronidazole [letter]. S Afr Med J 1983; 63:836.
8. Scott AK. Warfarin usage. Can safety be improved? Pharmacol Ther 1989; 42:429–57.
9. Qureshi GD, Reinders TP, Swint JJ, et al. Acquired warfarin resistance and weight-reduced diet. Arch Intern Med 1981; 141:507–9.
10. Kempin SJ. Warfarin resistance caused by broccoli [letter]. N Engl J Med 1983; 308:1229–30.
11. Karlson B, Leijd B, Hellstrom K. On the influence of vitamin K–rich vegetables and wine on the effectiveness of warfarin treatment. Acta Med Scand 1986; 220:347–50.
12. Aranko K, Seppala T, Pellinen J, et al. Interaction of diazepam or lorazepam with alcohol. Psychomotor effects and bioassayed serum levels after single and repeated doses. Eur J Clin Pharmacol 1985; 28:559–65.
13. Sato J, Nakata H, Owada E, et al. Influence of usual intake of dietary caffeine on single-dose kinetics of theophylline in healthy human subjects. Eur J Clin Pharmacol 1993; 44:295–8.
14. Neuvonen PJ, Kivisto KT, Lehto P. Interference of dairy products with the absorption of ciprofloxacin. Clin Pharmacol Ther 1991; 50:498–502.
15. Neuvonen PJ, Kivisto KT. Milk and yogurt do not impair the absorption of ofloxacin. Br J Clin Pharmacol 1992; 33:346–8.
16. Yuk JH, Nightingale CH, Sweeney KR, et al. Relative bioavailability in healthy volunteers of ciprofloxacin administered through nasogastric tube with or without enteral feeding. Antimicrob Agents Chemother 1989; 33:1118–20.
17. Hopkins S. Clinical toleration and safety of azithromycin. Am J Med 1991; 91(suppl 3A):40–5.
18. Randinitis EJ, Sedman AJ, Welling PG, et al. Effect of a high-fat meal on the bioavailability of a polymer-coated erythromycin particle tablet formulation. J Clin Pharmacol 1989; 29:79–84.
19. Alper MM, Barwin BN, McLean WM, et al. Systemic absorption of metronidazole by vaginal route. Obstet Gynecol 1985; 65:781–4.
20. Buening MK, Wold JS. Ethanol-moxalactam interactions in vivo. Rev Infect Dis 1982; 4(suppl):555–63.
21. Ward A, Richards DM. Cefotetan: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. Drugs 1985; 30:382–426.
22. Buening MK, Wold JS, Israel KS, et al. Disulfiram-like reaction to beta-lactam [letter]. JAMA 1981; 245:2027.
23. Pellock JM, Howell J, Kendig EL, et al. Pyridoxine deficiency in children treated with isoniazid. Chest 1985; 87:658–61.
24. Anonymous. Vitamin supplements. Med Lett Drugs Ther 1985; 27:66–8.
25. American Thoracic Society and Centers for Disease Control. Treatment of tuberculosis and tuberculosis infection in adults and children. Am Rev Respir Dis 1986; 134:355–63.
26. Hartman NR, Yarchoan R, Pluda JM, et al. Pharmacokinetics of 2′,3′-dideoxyinosine in patients with severe human immunodeficiency infection: II. The effects of different oral formulations and the presence of other medications. Clin Pharmacol Ther 1991; 50:278–85.
27. Bodey GP. Topical and systemic antifungal agents. Med Clin North Am 1988; 72:637–60.
28. Rodin SM, Johnson BF. Pharmacokinetic interactions with digoxin. Clin Pharmacokinet 1988; 15:227–44.
29. Mantyla R, Mannisto PT, Vuorela A, et al. Impairment of captopril bioavailability by concomitant food and antacid intake. Int J Clin Pharmacol Ther Toxicol 1984; 22:626–9.
30. Salvetti A, Pedrinelli R, Magagna A, et al. Influence of food on acute and chronic effects of captopril in essential hypertensive patients. J Cardiovasc Pharmacol 1985; 7(suppl):25–9.
31. Ohman KP, Kagedal B, Larsson R, et al. Pharmacokinetics of captopril and its effects on blood pressure during acute and chronic administration and in relation to food intake. J Cardiovasc Pharmacol 1985; 7(suppl):20–4.
32. Maslowski AH, Nicholls MG, Ikram H, et al. Haemodynamic, hormonal, and electrolyte responses to withdrawal of long-term captopril treatment for heart failure. Lancet 1981; 2:959–61.
33. Romankiewicz JA, Brogden RN, Heel RC, et al. Captopril: an update review of its pharmacological properties and therapeutic efficacy in congestive heart failure. Drugs 1983; 25:6–40.
34. Bailey DG, Munoz C, Spence JD, et al. Interaction of citrus juices with felodipine and nifedipine. Lancet 1991; 337:268–9.
35. Edgar B, Bailey D, Bergstrand R, et al. Acute effects of drinking grapefruit juice on the pharmacokinetics and dynamics of felodipine—and its potential clinical relevance. Eur J Clin Pharmacol 1992; 42:313–7.
36. Richter WO, Jacob BG, Schwandt P. Interaction between fibre and lovastatin. Lancet 1991; 338:706.
37. Davidson MH, Dugan LD, Burns JH, et al. The hypocholesterolemic effects of β-glucan in oatmeal and oat bran. JAMA 1991; 265:1833–9.
38. Bell LP, Hectorn KJ, Reynolds H, et al. Cholesterol-lowering effects of soluble-fiber cereals as part of a prudent diet for patients with mild to moderate hypercholesterolemia. Am J Clin Nutr 1990; 52:1020–6.
39. Howard PA, Hannaman KN. Warfarin resistance linked to enteral nutrition products. J Am Diet Assoc 1985; 85:713–5.
40. Martin JE, Lutomski DM. Warfarin resistance and enteral feedings. J Parenter Enter Nutr 1989; 13:206–8.
41. Petretich DA. Reversal of Osmolite–warfarin interaction by changing warfarin administration time [letter]. Clin Pharm 1990; 9:93.
42. Blickstein D, Shaklai M, Inbal A. Warfarin antagonism by avocado. Lancet 1991; 337:914–5.
43. Kappas A, Anderson KE, Conney AH, et al. Influence of dietary protein and carbohydrate on antipyrine and theophylline metabolism in man. Clin Pharmacol Ther 1976; 20:643–53.
44. Fagan TC, Walle T, Oexmann MJ, et al. Increased clearance of propranolol and theophylline by high-protein compared with high-carbohydrate diet. Clin Pharmacol Ther 1987; 41:402–6.

45. Jonkman JH. Food interactions with sustained release theophylline preparations. A review. Clin Pharmacokinet 1989; 16:162–79.

46. Jonkman JH, Sollie FA, Sauter R, et al. The influence of caffeine on the steady-state pharmacokinetics of theophylline. Clin Pharmacol Ther 1991; 49:248–55.

47. Johansson O, Wahlin-Boll E, Lindberg T, et al. Opposite effect of carbohydrate and protein on phenytoin absorption in man. Drug Nutr Interact 1983; 2:139–44.

48. Longe RL, Smith OB. Phenytoin interaction with an oral enteral feeding results in loss of seizure control. J Am Geriatr Soc 1988; 36:542–4.

49. Baurer LA. Interference of oral phenytoin absorption by continuous nasogastric feedings. Neurology 1982; 32:570–2.

50. Hooks MA, Longe RL, Taylor AT, et al. Recovery of phenytoin from an enteral nutrient formula. Am J Hosp Pharm 1986; 43:685–8.

51. Jann MW, Bean J, Fidone GS. Interaction of dietary pudding with phenytoin [letter]. Pediatrics 1986; 78:952–3.

52. Biale Y, Lewenthal M. Effect of folic acid supplementation on congenital malformations due to anticonvulsant drugs. Eur J Obstet Gynaecol Reprod Biol 1984; 18:211–6.

53. Brien MDO, Gilmour-White S. Epilepsy and pregnancy. BMJ 1993; 307:492–5.

54. Berg MJ, Fischer LJ, Rivey MP, et al. Phenytoin and folic acid interaction: a preliminary report. Ther Drug Monit 1983; 5:389–94.

55. Rivey MP, Schottelius DD, Berg MJ. Phenytoin-folic acid: a review. Drug Intell Clin Pharm 1984; 18:292–301.

56. Hahn TJ, Hendin BA, Scharp CR, et al. Effect of chronic anticonvulsant therapy on serum 25-hydroxycholecalciferol levels in adults. N Engl J Med 1972; 287:900–4.

57. Nutt JG, Woodward WR, Hammerstad JP, et al. The "on-off" phenomenon in Parkinson's disease. Relation to levodopa absorption and transport. N Engl J Med 1984; 310:483–8.

58. Baruzzi A, Contin M, Riva R, et al. Influence of meal ingestion time on pharmacokinetics of orally administered levodopa in parkinsonian patients. Clin Neuropharmacol 1987; 10:527–37.

59. Eriksson T, Granerus AK, Linde A, et al. "On-off" phenomenon in Parkinson's disease: relationship between dopa and other large neutral amino acids in plasma. Neurology 1988; 38:1245–8.

60. Brown C, Taniguchi G, Yip K. The monoamine oxidase inhibitor–tyramine interaction. J Clin Pharmacol 1989; 29:529–32.

61. Schulz R, Antonin KH, Hoffmann E, et al. Tyramine kinetics and pressor sensitivity during monoamine oxidase inhibition by selegiline. Clin Pharmacol Ther 1989; 46:528–36.

62. Anonymous. Food interacting with MAO inhibitors. Med Lett Drugs Ther 1989; 31:11–2.

63. Murphy DL. Monoamine oxidase–inhibiting antidepressants: a clinical update. Psychiatr Clin North Am 1984; 7:549–62.

64. Liu LX, Rustgi AK. Cardiac myonecrosis in hypertensive crisis associated with monoamine oxidase inhibitor therapy. Am J Med 1987; 82:1060–3.

65. Brown CS, Bryant SG. Monoamine oxidase inhibitors: safety and efficacy issues. Drug Intell Clin Pharm 1988; 22:232–5.

66. Jeppsson J, Sjogren J. The influence of food on side effects and absorption of lithium. Acta Psychiatr Scand 1975; 51:285–8.

67. Fleming BJ, Genuth SM, Gould AB, et al. Laxative-induced hypokalemia, sodium depletion and hyperreninemia. Ann Intern Med 1965; 83:60–2.

68. Brunton LL. Agents affecting gastrointestinal water flux and motility, digestants, and bile acids. In: Goodman and Gilman's The pharmacological basis of therapeutics. 8th ed. New York, NY: Macmillan Publishing, 1990:921.

69. Clark JH, Russell GJ, Fitzgerald JF, et al. Serum beta-carotene, retinol, and alpha-tocopherol levels during mineral oil therapy for constipation. Am J Dis Child 1987; 141:1210–2.

70. Roe DA. Therapeutic significance of drug-nutrient interactions in the elderly. Pharmacol Rev 1984; 36(suppl 2):109–22.

71. Roe DA. Nutrient and drug interactions. Nutr Rev 1984; 42:141–54.

72. Wernicke JF, Dunlop SR, Dorndeif BF, et al. Fixed-dose fluoxetine therapy for depression. Psychopharmacol Bull 1987; 23:164–8.

73. Kinney-Parker JL, Smith D, Ingle SF. Fluoxetine and weight: something lost and something gained? Clin Pharm 1989; 8:727–33.

74. Morrison SD. Origins of anorexia in neoplastic disease. Am J Clin Nutr 1978; 31:1104–7.

75. Anonymous. Drug of choice for chemotherapy. Med Lett Drugs Ther 1993; 35:43–50.

76. Pyke DA, Leslie RDG. Chlorpropamide-alcohol flushing: a definition of its relation to non-insulin dependent diabetes. BMJ 1978; 2:1521–2.

77. Seltzer H. Drug-induced hypoglycemia. A review of 1418 cases. Endocrinol Metab Clin North Am 1989; 18:163–83.

78. Seppala T, Linnoila M, Elonen E, Mattila MJ, Maki M. Effects of tricyclic antidepressants and alcohol on psychomotor skills related to driving. Clin Pharmacol Ther 1975; 17:515.

79. Freed E. Alcohol-triggered neuroleptic-induced tremor, rigidity and dystonia [letter]. Med J Aust 1981; 2:44–5.

80. Saario I, Linnoila M. Effect of subacute treatment with hypnotics, alone or in combination with alcohol, on psychomotor skills related to driving. Acta Pharmacol Toxicol 1976; 38:382–92.

81. Smith CH, Bidlack WR. Dietary concerns associated with the use of medications. J Am Diet Assoc 1984; 84:901–13.

82. Williams L, Davis JA, Lowenthal DT. The influence of food on the absorption and metabolism of drugs. Med Clin North Am 1993; 77:815–29.

83. USPDI: drug information for health care professionals. 15th ed. Rockville, Md: The United States Pharmacopeial Convention, Inc, 1995.

84. Olin BR, ed. Drug facts and comparisons. St Louis, Mo: JB Lippincott, 1995.

85. CCIS (R) system: computerized clinical information system. Englewood, Colo: Micromedex, Inc, 1994 (edition expiration date: 2/28/95).