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EFFECTS OF FOOD ON DRUG ABSORPTION

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ABSTRACT

This chapter provides an update on drug-food interactions reported in the literature during the past five years. The number of studies examining this phenomenon has increased dramatically, and many of the results of these studies have been unpredictable and spectacular. Drug-food interactions should really be considered as formulation-food interactions because of increasing evidence that a drug may be affected differently by food when it is administered in different formulations. Drug-food interactions may be classified into five categories: those causing reduced, delayed, increased, and accelerated absorption, and those in which food has no effect. While it continues to be necessary to examine drug-food interactions for specific drugs and drug formulations, additional avenues need to be explored to seek mechanistic patterns that may lead to better prediction of the nature and extent of changes in circulating drug levels due to the presense of food, and their possible clinical impact.

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INTRODUCTION

How food affects drug absorption is a subject that did not achieve full recognition in scientific and regulatory circles until 1977, when the first major

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review on this topic was published (199). Since that time, the number of studies examining various aspects of food-drug interactions has increased, and the topic has been extensively reviewed, both in terms of interactions of particular drugs or families of drugs (142, 177, 200, 201, 203, 211), and in terms of relating the effects of those interactions to clinical consequences (99, 129, 131, 215).

The ultimate goal of these studies has been to understand the mechanisms involved in drug-food interactions, and also to use these data to establish guidelines to predict outcomes. However, this goal has proven elusive. After almost 20 years of research, it is still not possible to predict the outcome of drug-food interactions with respect to circulating drug and/or metabolite levels. Drug-food interactions are influenced both by the nature of the food and also by the formulation in which a drug is administered.

Food

The type and size of a meal may have a marked effect on the nature of a drug-food interaction. Liquid meals, which are often used in an attempt to obtain mechanistic information, might have a totally different effect on drug absorption compared with solid meals, which are nonetheless more clinically relevant. The time interval between eating and medication will also affect the nature and extent of a drug-food interaction.

Dosage Form

Many studies have demonstrated that formulation may have a dramatic effect on drug-food interactions. The preponderance of evidence shows that the more disperse a drug formulation, the less effect food will have. Drugs administered in solution are likely to be much less affected by food than are drugs formulated into a compressed tablet.

INFLUENCE OF FOOD ON THE GASTROINTESTINAL TRACT

In the fasting state, gastric motility passes through cycles of migrating motor complexes (MMC). Each cycle lasts 2–3 h and comprises four phases, of which phase 3, the "housekeeper wave," is the strongest. Non-nutrient liquids pass through the stomach largely independent of MMC, but solids are moved from the stomach into the small intestine mainly during phase 3. Depending on when a solid meal is ingested relative to the MMC, the gastric residence time may vary from a few minutes to 2–3 h (50). Ingested food changes gastric motility to a postprandial pattern, during which time gastric residence time is increased,

particularly by solid meals and by chyme of low pH, high osmolality, and high-fat content. Residence time is also influenced by hot meals.

Although solid foods tend to delay gastric emptying, non-nutrient liquid meals may have the opposite effect. As described previously (199), the stomach appears to empty liquid meals into the duodenum in first-order fashion. Distension of the stomach is the only natural stimulus known to increase stomach emptying. The observation that the stomach empties at a faster rate with increasing fluid volume can be rationalized in terms of varying tension at receptors in the stomach wall (78). The presence of ingested food also promotes gastric secretion of hydrochloric acid.

Once food passes from the stomach into the small intestine, it has a stimulating effect on intestinal motility, on digestive enzyme secretion and also, particularly in the case of fatty meals, on bile secretion.

The influences of altered gastric and intestinal motility, the one decreased and the other increased, as well as increasing gastrointestinal (GI) secretions with ingested food, might be expected to have a number of effects on drug absorption. Delayed gastric emptying will delay absorption of those drugs that are absorbed predominantly from the small intestine but not of those that are absorbed from the stomach. It will delay absorption of acidic compounds or drugs in enteric-coated formulations by delaying drug transit from the acidic contents of the stomach to the relatively alkaline region of the small intestine. On the other hand, delayed gastric emptying might increase systemic availability of compounds that have poor solubility at acidic gastric pH by permitting more material to dissolve in the stomach before passing into the small intestine. Compounds that are unstable in acidic pH are likely to be degraded as a result of prolonged residence in the stomach.

It has already been noted that large volumes of non-nutrient fluids empty from the stomach at a faster rate than small volumes do. The large volume itself tends to accelerate dissolution and also transfer of both dissolved and undissolved drug from the stomach into the small intestine. The presence of large fluid volumes in the intestine may continue to increase drug absorption by providing a more liquid environment and also by a solvent drag effect. On the other hand, larger fluid volumes might be expected to delay absorption because of a low serosal-mucosal drug concentration gradient.

Ingested food may affect splanchnic blood flow, but the degree and direction of change may vary with the type of food (138, 179). A high protein meal has been shown to cause a 35% increase in splanchnic blood flow, whereas a liquid glucose meal caused an 8% decrease. In most cases after solid meals, one would expect splanchnic blood flow to increase (113) to promote drug absorption via the splanchnic circulation. How much drug enters the systemic circulation is a function also of presystemic clearance. The most common food effect has been that of increased drug systemic availability associated with

reduced presystemic clearance, for example, propranolol, hydralazine, metoprolol, and propafenone (4, 117). Food may also exert a direct influence on intrinsic drug metabolism, both presystemic and systemic. For example, oxidative metabolism may be increased by high-protein diets or by diets high in cruciferous vegetables. Grapefruit juice has been shown to inhibit the metabolism of dihydropyridine calcium channel blockers. Systemic availability of orally administered felodipine was increased more than twofold by coadministered grapefruit juice (5). A less-pronounced effect was observed with nifedipine. This effect may be linked to inhibition of cytochrome P-450 IIIA4 by flavonoids present in grapefruit juice.

DIRECT EFFECT OF FOOD ON DRUG ABSORPTION

In addition to the indirect effects on GI physiology, food may also affect drug absorption directly. Food may act as a physical barrier inhibiting drug dissolution and preventing drug access to the mucosal surface of the GI tract. Specific ions or other substances in food may cause reduced drug absorption, for example chelation of tetracycline and penicillamine by metal ions, or from interaction with proteins. For drugs that are actively absorbed, a direct competition for active carriers may occur between protein fragments and drug molecules, giving rise to decreased drug systemic availability.

Drug-food interactions are a particular problem for oral controlled-release products. These delivery devices present a greater quantity of drug to the patient per single dose unit than conventional dosage forms do and are designed to deliver the drug at a controlled rate over a prolonged period. With these formulations, a marked effect by administered food on systemic availability may have a serious and prolonged effect on circulating drug levels.

The following section is divided into recent reports of concomitant food giving rise to reduced, delayed, and increased drug absorption. It also discusses cases where food has no significant effect on drug absorption.

REDUCED DRUG ABSORPTION

Drugs whose absorption is reduced by food are listed in Table 1.

Alendronate sodium is a potent biophosphonate currently being studied for use in the treatment of osteoporosis. The systemic bioavailability of alendronate sodium is approximately 0.75%, with considerable intra- and intersubject variation (60). Absorption is further reduced by approximately 40% when the drug is taken 1–2 h before ingestion of food, and by as much as 90% when taken up to 2 h after food ingestion. These observations led to a recommendation that alendronate be taken after overnight fast, at least 30 min before food. Although no explanation was offered for reduced absorption of the

Table 1 Drugs whose absorption is reduced by food

Drug	Ref.	Drug	Ref.
Alendronate Sodium	60	Naproxen	139
Ambenonium chloride	137	Navelbine	108
Atenolol	9	Nitrendipine	204
Azithromycin	41	Norfloxacin	90
Cefprozil	125	Paracetamol	147
Ceftibuten	83	Phenytoin	183
2-Choro-2′-deoxyadenosine	1	Pravastatin	140
Cicaprost	14	RO 42-5892	197
Ciprofloxacin	131	Rufloxacin	168
Didanosine	93, 174	SK & F 106203	132
Dideoxycytidine	128	Sotalol	68
Doxazosin	27	Sulpiride	172
Flecainide	159	Tacrine	205
Hydralazine	169	Tetracycline	28
Levodopa, carbidopa	156	Verapamil	76
Metformin	18	Zidovudine	107, 158, 190, 191
Methotrexate	44	882C	141
MK-679	218		

already poorly absorbed alendronate in the presence of food, it was noted that alendronate forms insoluble complexes with multivalent cations such as Ca^{2+} and Mg^{2+}.

Dramatic reduction is reported in serum levels of the cholinesterase inhibitor ambenonium chloride by food in patients with myasthenia gravis (137). Peak serum concentrations (C_{max}) and the area under the serum concentration profile (AUC) from 0 to 3 h after dosing [AUC(0–3 h)] were both reduced by 70% after ingestion of a conventional breakfast compared with during the fasting state, whereas the time of peak concentration (t_{max}) was moderately increased. Mean serum-time curves following single 10-mg doses of ambenonium chloride are shown in Figure 1. Despite this rather dramatic food effect, relationships between serum drug levels and relative clinical effect (changes in muscle strength) were variable and inconclusive.

The very hydrophilic atenolol molecule differs from the lipophilic compounds of this class, metoprolol and propranolol, in that its absorption is reduced by food (9, 118). The mechanism by which food decreases atenolol absorption was addressed in a study conducted with healthy volunteers who received single doses of a commercial tablet, or of a capsule containing bile acids (9). The bile acid formula reduced mean atenolol plasma C_{max} by 28% and AUC by 30% relative to commercial tablets. It is claimed that bile acids reduce systemic availability of atenolol to a similar or greater extent than that

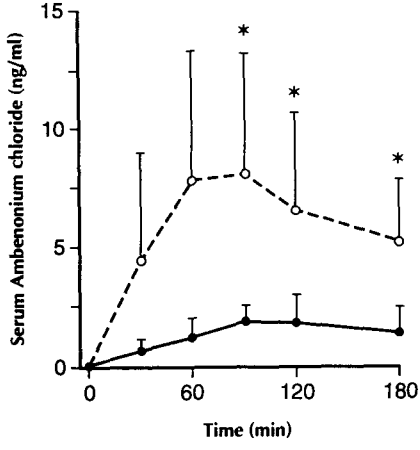

Figure 1 Mean serum versus time concentrations (±standard error) of ambenonium chloride after oral administration of 10 mg of ambenonium chloride to six myasthenia gravis patients under fasting (*open circles*) and nonfasting (*closed circles*) conditions. *, $P < 0.05$. (Reproduced with permission from Reference 137.)

previously reported for ingested food. Previous studies have shown that bile acids can increase (25) and decrease (217) drug absorption. The use of different formulations in the present study make the data difficult to interpret. The systemic oral availability of the azalide antibacterial agent azithromycin is approximately 30% (41). Coadministration of azithromycin with a large meal may further reduce absorption by up to 50%. The mechanism of this interaction is unknown, but this basic, highly lipid-soluble compound is degraded by acid-catalyzed hydrolysis of the ether bond to the neutral cladinose sugar (52), which may contribute to its poor oral bioavailability.

Two studies have demonstrated reduced absorption of new cephalosporins in the presence of food (125), or an elemental diet (83). Administration of cefprozil to children after a meal caused a 22% reduction in mean C_{max} values and a 16% reduction in urinary excretion of cefprozil. Simultaneous administration of ceftibuten with an elemental diet composed of egg white hydrolysate, with an elemental diet composed of amino acids, or with a mineral solution had a similar effect. Studies of rats confirmed the effect these test meals had on ceftibuten absorption.

Food moderately reduced the systemic availability of 2-chloro-2′-deoxyadenosine in patients with leukemia (1). Reduced systemic availability in the presence of food may be related to slower absorption, resulting in a greater proportion of absorbed drug undergoing presystemic metabolism. Reduced

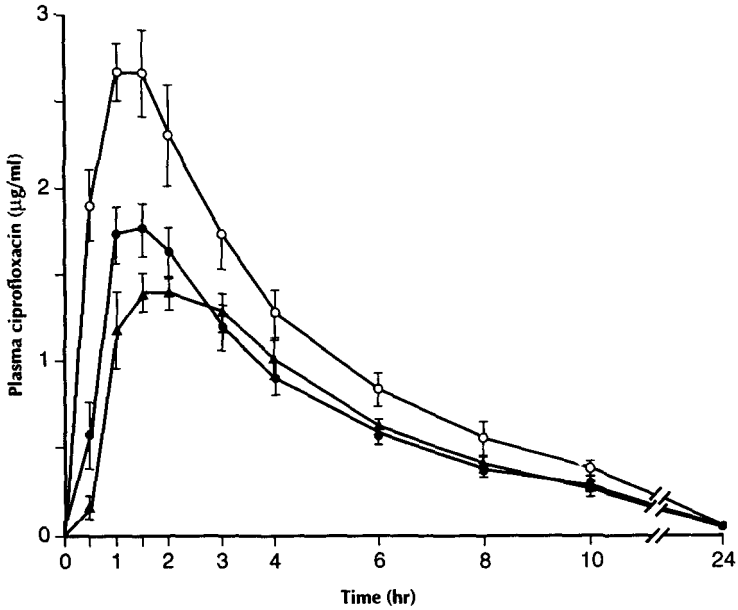

Figure 2 Mean plasma versus time concentrations (±standard error) of ciprofloxacin in seven subjects following a single 500-mg oral dose of ciprofloxacin with 300 ml of milk (*closed circles*), yogurt (*triangles*), or water (*open circles*). (Reproduced with permission from Reference 131.)

absorption due to food may be a possible explanation for reduced antiplatelet activity of cicaprost (14). Although neither a standard breakfast nor a high-fat, high-calcium breakfast altered ciprofloxacin absorption (56), absorption was markedly impaired by coadministered milk and yogurt (131). Systemic availability was reduced 35% by coadministered milk and yogurt compared to water. Thus, ciprofloxacin is affected by dairy products to a similar extent as tetracycline derivatives (116). Plasma levels of ciprofloxacin taken with milk, yogurt, and water are shown in Figure 2. Ciprofloxacin, together with other fluoroquinolones, is known to bind with heavy metals, including calcium, to form an insoluble chelate (73, 121).

Food ingestion had a marked effect on the absorption of the purine nucleoside analogue didanosine in men seropositive for human immunodeficiency virus (HIV) but free of AIDS symptoms (93). Decreased bioavailability after postprandial administration may have been due to prolonged gastric retention, leading to increased degradation of the acid-labile didanosine. In a separate study, the bioavailability of didanosine from a chewable tablet was reduced

approximately twofold in the presence of a standardized breakfast (174). These results led to the recommendation that didanosine be administered under fasting conditions.

A milder food effect was reported for the novel quinazoline antihypertensive agent doxazosin. Mean C_{max} in hypertensive subjects was reduced 18%, and the AUC was reduced by 12%, after intake of a standardized light breakfast compared with during fasting. A more significant clinical effect with flecainide was possibly attributed to a milk-drug interaction (159). Toxicity in the form of ventricular tachycardia occurred in a baby boy when dextrose was substituted for milk foods during flecainide therapy. Serum flecainide levels, based on single point determinations, were doubled from 990 to 1824 mg/ml 24 h following dextrose substitution. This effect justifies close flecainide blood monitoring in infants who may be on intermittent milk diets.

Both a standard breakfast and a bolus enteral nutrient treatment gave rise to much lower blood levels of hydralazine compared with fasting and infusion of nutrients, although there was considerable inter-individual variation (169). Typically, the fasted treatment yielded a C_{max} value of 87 ng/ml compared with 11 and 15 ng/ml for the standard breakfast and enteral bolus treatments, respectively. This study shows that, for hydralazine at least, the physical form of nutrients may play an important role in the extent and nature of drug-food interactions.

Plasma levels of levodopa, 3-O-methyldopa, and carbidopa were compared from patients with idiopathic Parkinson's disease after taking a controlled release formulation containing 200/50 levodopa and carbidopa (156). Coadministration with a high-protein meal reduced plasma levels of both levodopa and carbidopa. However, concentrations of the levodopa metabolite 3-O-methyldopa increased in the presence of the high-protein meal. While levodopa and carbidopa levels were generally reduced by high-protein meals, the plasma levels exhibited a flattened concentration-effect profile.

The mean systemic availability of methotrexate was reduced 15% and C_{max} was reduced 38% in patients given the medication immediately after breakfast compared with while fasting (44). Mean absolute bioavailability of methotrexate in these patients was 90% in the fasting state and 77% after breakfast. Coadministered food reduced nitrendipine absorption in an efficacy study in juveniles with severe hypertension (204). C_{max} values were reduced from 71 to 13 ng/ml and AUC_{ss} values were reduced from 158 to 46 ng•h/ml, whereas t_{max} was increased from 1 to 2.4 h by food.

As noted previously with ciprofloxacin (131), coadministration with milk or yogurt markedly reduced the systemic availability of norfloxacin (90). C_{max} and the AUC(0–24 h) values were reduced by approximately 50% with milk or yogurt compared to water. Plasma profiles obtained in this study are shown in Figure 3. The results of this study provide further evidence that, while

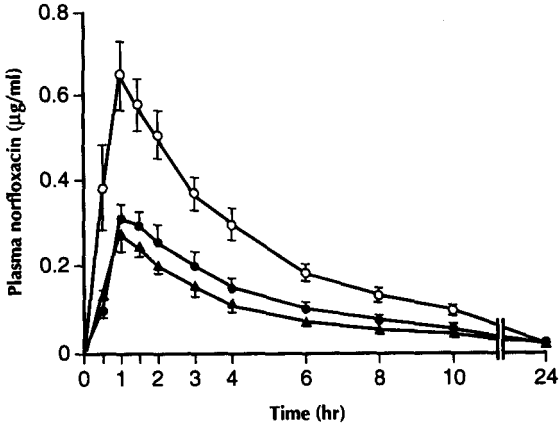

Figure 3 Mean plasma versus time concentrations (±standard error) of norfloxacin in seven subjects following a single 200-mg oral dose of norfloxacin with 300 ml milk (*closed circles*), yogurt (*triangles*), or water (*open circles*). (Reproduced with permission from Reference 90.)

absorption of oral fluoroquinolones is not affected to a significant extent by solid foods (192), dairy products containing solubilized calcium may reduce circulating drug levels to an extent that may well be clinically significant.

In a study in hypercholesterolemic men, pravastatin C_{max} dropped by 49% and AUC dropped by 31% in the presence of food compared with during the fasting state (140). However, reduction in mean total cholesterol and low density lipoproteins was identical whether pravastatin was taken under fasting or nonfasting conditions. The lack of effect on blood lipids may have been due to food causing increasing extraction of pravastatin by the liver, which is the primary site of cholesterol synthesis and clearance, and also of pravastatin activity.

The beta blocking agent sotalol appears to behave more like atenolol (9) than metoprolol or propranolol in that its oral bioavailability is reduced by approximately 20% by administered food. Like atenolol, sotalol undergoes negligible metabolism and any change in hepatic blood flow due to food is not likely to have a positive effect on oral availability.

Systemic availability of the cognition agent tacrine was reduced by approximately 20%, and peak plasma levels were reduced by 40% when the drug was administered following a standard breakfast (205). However, administration with meals reduced the incidence and severity of GI side-effects, thus improving patient tolerance. Absorption of tetracycline was depressed to a similar extent by a Mexican meal and a conventional western meal, although the Mexican meal contained double the amount of calcium (29).

A number of studies have examined the effect of food on the absorption of the HIV agent zidovudine (107, 158, 190, 191). All of these studies reported significantly delayed and reduced absorption, with consistency across studies. Typically, t_{max} is increased from 0.5 to 1.5–2.0 h, whereas C_{max} and AUC are decreased by approximately 50% when zidovudine is administered with a meal compared with during fasting. Although no direct relationship has been established between circulating levels and efficacy of zidovudine, doses found to be effective in AIDS patients generally achieve peak serum levels of ≥0.27 mg/ml. However, lower and more prolonged levels obtained after meals may maintain efficacy while reducing toxicity (191).

Food caused significant reduction in C_{max} and a modest reduction in AUC in healthy volunteers of 882C [1-(b-D-arabinofuranosyl)-5-(1-propynyl)uracil], which is being studied for use in the treatment of varicella zoster virus infections (141). The effects observed in this single-dose study led to the recommendation that effective concentrations of 882C can be maintained without food restrictions.

INTERACTIONS CAUSING DELAYED DRUG ABSORPTION

Compounds whose absorption is delayed by food are listed in Table 2.

Delayed absorption may be considered unimportant for the majority of drugs, whose circulating drug profiles in the nonfasted state would be simply offset in time relative to those in the fasted state. However, the importance of an interaction depends on its extent and also on the drug therapeutic index. Peak circulating levels of some drugs in Table 2 are reduced by up to 60% with food ingestion, and changes of this magnitude are likely to be therapeutically important.

Minor delays in circulating levels of acetorphan (15) and albuterol (81) due to food are probably clinically unimportant, whereas a 50% reduction in aniracetam C_{max} for aniracetam by food is likely to have clinical consequences (75, 155). Possible clinical significance is claimed for the delay in beta-methyldigoxin absorption by food (189). Mean serum beta-methyldigoxin C_{max} levels were reduced from 1.79 ng/ml when the drug was taken during fasting to 0.96 ng/ml when the drug was taken 30 min after ingestion of food. The results obtained with beta-methyldigoxin are similar to those reported for digoxin (86, 164).

A number of studies have examined and compared the effects of ingested food on oral cephalosporins. Absorption of cefaclor was delayed following rice and bread meals (135), the effect increasing with meal size. Similar delays in absorption were observed when cefactor was taken immediately after a

Table 2 Drugs whose absorption is delayed by food

Drug	Ref.	Drug	Ref.
Acetorphan	15	Loracarbef	33, 154
Albuterol	81	Methotrexate	98, 134
5-Aminosalicylic acid	32	Monofluorophosphate	196
Aniracetam	75, 155	Moricizine	145
Beta-methyldigoxin	189	Nicorandil	57
Cefaclor	8, 135	Nifedipine	149
Cefdinir	122, 124	Ofloxacin	43, 130
Cefprozil	8, 173	Paracetamol	195, 206
CL 275838	26	Penciclovir (famciclovir prodrug)	53, 54
Diclofenac	184, 186	Rifabutin	127
Diltiazem	208	Salsalate	70
Doxycycline	210	Terazocin	114
Erythromycin acistrate	85	Terfenadine	49
Fadrozole	22	Theophylline	88, 221
Famotidine	115	Tiagabine	119
Flurbiprofen	40	Topiramate	38
Fluvastatin	176	Trazodone	133
Fusidate sodium	110	Valproic Acid	136
Hydroxychloroquine	112	Vigabatrin	72
Isosorbide-5-mononitrate	96	Zalospirone	95
Lomefloxacin	77	Zidovudine	160, 171

standard breakfast, yielding a 51% reduction in mean C_{max} values (8). Peak levels of cefprozil were unaffected under the same study conditions. Other studies have shown cefadroxyl to be unaffected by food, whereas absorption of cephalexin is delayed similar to that of cefaclor (105). Peak plasma levels of cefdinir were reduced approximately 50% by food in children who received the drug as a fine granule suspension (122, 124). No reduction in C_{max} occurred; in fact, the mean C_{max} value increased from 0.61 mg/ml during fasting to 0.79 mg/ml in the fed state in infants who received a 3-mg/kg pediatric dose.

Coadministered food had a marked effect on circulating levels of diclofenac. Absorption from a 150-mg hydrogel bead capsule in healthy male subjects was delayed, yielding a mean C_{max} value of 312 ng/ml at 6.25 h compared to 502 ng/ml at 2 h in the fasted state (186). The results obtained by using diclofenac capsules are in contrast to those obtained by using diclofenac enteric-coated tablets in which peak circulating levels were delayed but not reduced by food (185, 213).

Results obtained in a food-effect study with erythromycin acistrate (2′-acetyl erythromycin stearate) are consistent with earlier reports on erythromycin and its derivatives (85). Food generally reduces systemic availability of erythromycin and erythromycin stearate (203), whereas absorption of erythromycin

esters is either unchanged or increased (202). The rate of erythromycin acistrate absorption was delayed to a small extent following a light meal and to a greater extent following a heavy meal. While the effect was attenuated after repeated doses, food significantly delayed absorption in some individuals, resulting in undetectable levels up to 24 h postdosing. Data supporting the influence that stomach emptying time has on drug absorption rate are provided by a study in which flurbiprofen tablets were administered with equal volumes of water or calorie-dense apple juice (40). Apple juice significantly increased mean gastric emptying time, from 57 min in the fasted state to 102 min in the fed state. Studies of healthy male subjects showed that food can markedly affect circulating levels of the hydroxymethylglutaryl-coenzyme A reductase inhibitor fluvastatin (176). Peak plasma levels were reduced by 70% and t_{max} was increased fourfold by ingestion of a standard low-fat breakfast following a solution dose of fluvastatin, whereas peak levels were reduced 55% and t_{max} values increased up to fourfold by a capsule dose. A similar but somewhat attenuated effect was observed following a low-fat evening meal. Efficacy data following the evening dose study showed no significant difference in reduction in total cholesterol and low density lipoproteins-cholesterol between fed and fasted subjects. A substantial food effect is reported for the oral beta-lactam antibiotic loracarbef (33). Although systemic availability was similar in subjects who received 200-mg doses in fasting and nonfasting states, peak plasma levels were reduced over 50% and the time of peak was doubled by food. In the same study, the area under the loracarbef serum curve was approximately doubled by coadministered probenecid, and elimination half time ($t_{1/2}$) was increased from 1 to 1.5 h.

Two studies examined the effect of food on bioavailability of methotrexate. The first study examined the effect of a standard high-fat breakfast on absorption of methotrexate from 7.5-mg tablet doses. Postprandial administration resulted in a 16% reduction in peak plasma levels and a 30-min delay in t_{max}. Greater effect was observed when methotrexate was given during fasting or after a standard French breakfast in patients with rheumatoid arthritis (134). C_{max} was reduced by 31% and t_{max} was increased by 40 min. Absolute systemic availability varied from 28 to 94% relative to intravenous methotrexate and was not influenced by food. A more dramatic effect was obtained when fluoride in the form of monofluorophosphate was administered after a standard meal compared with during fasting (196). Food caused a 67% reduction in peak plasma fluoride levels. AUC and urinary excretion values were essentially unchanged.

A high-fat meal markedly reduced the absorption rate of the calcium channel blocking agent nifedipine (149), reducing peak plasma levels by 47%. The related compounds nicardipine and nitrendipine were unaffected by food. Milk and yogurt had only small effect on ofloxacin absorption (43, 130), while a

standard meal caused a 20% reduction in peak plasma levels and a moderate delay in t_{max}. Ofloxacin is thus similar to other fluoroquinolone antibiotics in that it is only modestly affected by food and can generally be administered without regard to meals.

Food decreased the absorption rate of salicylsalicylic acid (70). However, the effect was modest, and there was essentially no effect on circulating levels of the major metabolite salicylic acid. A modest effect is also reported for terazosin, whose absorption was moderately delayed by food, giving rise to a 23% reduction in C_{max} and a 0.9-h increase in t_{max} (114). The maximal fall in standing blood pressure after ingestion of food was similar to that during the fasting state. Minor food effects were observed with terfenadine, peak levels of the active metabolite decreasing only 13% following ingestion of a standard high-fat breakfast compared with during fasting (49).

Two studies have contributed further to the spectrum of food effects reported for theophylline. Absorption of theophylline from Theo-Dur® tablets was delayed to a small extent, but mean peak levels increased from 4.7 to 6.3 mg/ml from a postprandial evening dose compared with during the fasting state. The increase in C_{max}, together with observed intersubject variability in serum profiles obtained following evening doses, may have implications for patients who require consistent medication at night. In a second study, the rate of theophylline absorption from a multiparticulate controlled release formulation was delayed (221). Following both fed and fasting treatments, 37–39% of the absorbed dose was absorbed from the colon, showing this to be an important absorption site, at least for sustained-release products of theophylline.

A study on valproate pharmacokinetics shed some light on the influence of food on apparent circadian rhythm in absorption of this and possibly other compounds (136). Valproate was administered to healthy male subjects following conventional light breakfast and heavy evening meals and also following identical morning and evening meals. Following the light breakfast/heavy evening meal doses, absorption of valproate was delayed following the evening dose relative to the morning dose. When valproate was administered following identical morning and evening meals, there were no differences in the resulting plasma valproate profiles. These results lead to speculation as to what extent different food effects may have contributed to circadian rhythm effects previously reported for other drugs.

Different meals influenced the extent of drug-food interaction with the serotonin agonist/antagonist zalospirone (95). Administration of a single zalospirone dose after a meal containing 43% fat resulted in a 31% reduction in peak drug levels compared with during the fasting state. Administration after a meal containing 19% fat resulted in only a 13% reduction. Peak drug levels were delayed twice as long after the high-fat meal compared to the low-fat meal.

In a study in 18 asymptomatic HIV-infected subjects, zidovudine C_{max} was reduced 57 and 47% when zidovudine was administered 30 min and 3 h after ingestion of a high-fat breakfast (171). In a second study of symptomatic HIV-infected men, serum zidovudine C_{max} was reduced 32% when the drug was administered after a liquid protein meal relative to the fasted state (160). Absolute absorption values were unaffected. The different results obtained in these studies compared with those described in Table 1 present an excellent example of the unpredictable nature of drug-food interactions and of the hazards of basing conclusions on only one study from one laboratory.

INTERACTIONS CAUSING INCREASED DRUG ABSORPTION

Studies cited in Table 3 represent a substantial portion of the total number of reports on drug-food interactions. They reflect not only the broad spectrum of effects that may derive from drug-food interactions, these studies also reflect the frequent unpredictability of the interactions. The compounds in this section tend to be poorly water soluble, but this is not always the case. Some interactions are trivial while others are potentially clinically important.

To examine its absorption in the presence of food, amiodarone was administered into the jejunum with two nutrient solutions, one at the rate of 3.3 kcal/min and the other at the rate of 1.3 kcal/min (143). Absorption of amiodarone correlated significantly with lipid absorption rate. However, plasma C_{max} and AUC values were variable and tended to be higher from the 1.3-kcal/min infusion. These results were attributed to wide fluctuations in amiodarone pharmacokinetics, distribution, and metabolism.

Conflicting results were reported with the onchocerciasis agent amocarzine (CGP 6140) (101). In male Guatemalan patients, systemic availability increased 20% when the drug was taken with a copious breakfast compared with during fasting. When the dose was increased to 1200 mg, both the peak plasma levels and the systemic availability of amocarzine were increased approximately threefold when the drug was given after a standard breakfast, relative to fasting (100). The remarkable increase in absorption due to food after the high dose of amocarzine may be related to the greater degree of solubilization by the meal or to decreased presystemic metabolism. Substantially increased absorption due to food was reported for the lipophilic antiprotozol agent atovaquone (152). Peak atovaquone plasma levels increased over fivefold and systemic bioavailability increased over threefold when the drug was given after a high-fat breakfast compared with during fasting. Mean plasma profiles obtained over 48 and 528 h are shown in Figure 4. Complimentary studies using a variety of conditions led to the conclusion that the food effect with

Table 3 Drugs whose absorption is increased by food

Drug	Ref.	Drug	Ref.
Alprazolam	216	Itraconazole and fluconazole	222
Amiodarone	143	Levodopa	3, 209
Amocarzine	100, 101	5-Methoxypsoralen	47
Astemizole and pseudoephedrine	84	Moclobemide	24
Atovaquone	152	Nifedipine	5, 92
Bay-X-1005	12	Oxcarbazine	31
Brofaromine	30	Oxybutinin	219
Buflomedil	214	Phenytoin	67
Cefetamet pivoxil	17, 180	Progesterone	175
Cefuroxime	111	Repirinast	167
CGP 43371	178	Sparfloxacin	181
Clarithromycin	23, 59	S-1108	126, 161
Cyclosporine	64, 65	Theophylline	28
Danazol	20	Ticlopidine	170
Diltiazem	55	Tramadol	103
Encainide	71	Vanoxerine	82
Felodipine	5, 46	Vinpocetine	106
Fenretinide	39	Zalospirone	91
Gepirone	182	566C80	153
Itraconazole	10, 194		

atovaquone was probably due to combined effects of bile release and also to increased solubility resulting from the fatty meal.

Absorption of cefetamet pivoxil was delayed by food. Mean peak plasma levels occurred at 4.8 h compared to 3 h during fasting. Overall bioavailability and peak plasma levels increased approximately 25–30% (17). A similar effect was observed when cefetamet pivoxil was administered 1 h after a standard breakfast, although plasma profiles were similar when drug was administered with or before a standard breakfast (180).

Previous studies have shown that bioavailability of cefuroxime is increased by food (212). In a subsequent mechanistic study, hyoscine butylbromide had no effect on cefuroxime absorption whereas cholecystokinin resulted in a 20% increase in cefuroxime C_{max} and AUC values (111). These results lead to the conclusion that bile release, but not gastric emptying, may be at least partially responsible for increased cefuroxime absorption in the presence of food.

A remarkable food effect involved the lipophilic hypolipidemic compound CGP 43371 (178). Administration of single 800-mg capsule doses of CGP 43371 after breakfast caused an 11-fold increase in peak plasma drug levels

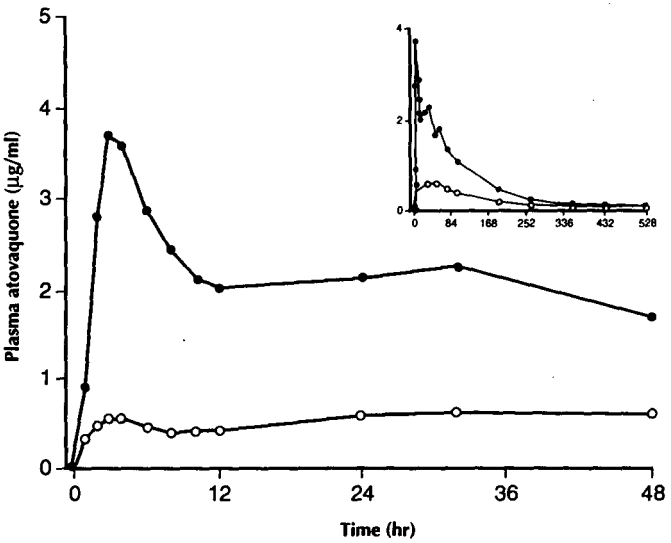

Figure 4 Mean plasma versus time concentrations of atovaquone in 18 subjects following a single 500-mg oral dose of atovaquone fasted (*open circles*) or 45 min after a high-fat meal (*closed circles*). (Reproduced with permission from Reference 152.)

and a 13-fold increase in overall bioavailability relative to the fasting state. Plasma levels from this study are shown in Figure 5.

As CGP 43371 is absorbed mainly from the ileum, delayed gastric emptying would enable more compound to disintegrate and dissolve before reaching this absorption site. It is proposed that CGP 43371 dosage should be modified relative to food intake.

Following a 7.5-mg/kg dose of the macrolide antibiotic clarithromycin to infants and children either fasting or after ingesting milk and/or hash brown potatoes, peak plasma levels were 4.6 and 3.6 mg/ml after nonfasting doses, respectively (59). Systemic availability increased by 40%. In a study of adults, food taken immediately before a 500-mg clarithromycin dose increased absorption by approximately 25% (23). In both of these studies, plasma levels of the major active metabolite 14-hydroxyclarithromycin were moderately increased.

Absorption of the heterocyclic steroid derivative danazol (20), and also of the retinoid fenretinide (39), is substantially increased by food. Systemic availability of danazol from a capsule dose was increased over threefold by food in healthy female subjects, whereas bioavailability and peak plasma levels of fenretidine increased threefold following a high-fat meal compared with during

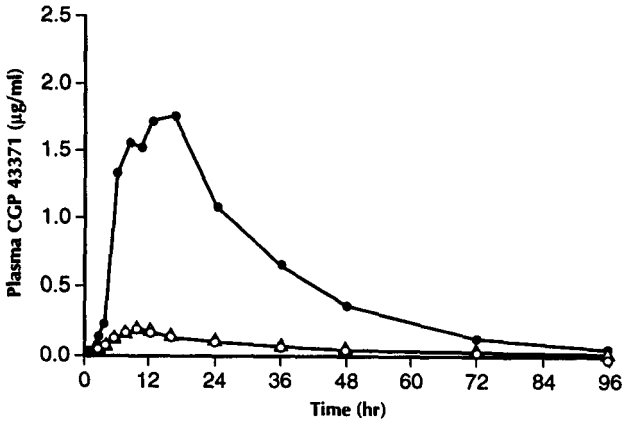

Figure 5 Mean plasma versus time concentrations of CGP 43371 in 12 subjects following a single 800-mg oral dose of CGP 43371 as a dispersion (*triangles*) or capsule (*open circles*) under fasting conditions or as a capsule after a standard meal (*closed circles*). (Reproduced with permission from Reference 178.)

fasting (39). Administration of fenretidine in an oil suspension to fasting subjects yielded intermediate values. Further examination of the effect of meal composition showed that a high-fat meal resulted in plasma fenretinide bioavailability three times greater than did a carbohydrate meal, with a high protein meal yielding intermediate results. Mean plasma profiles of fenrotidine are shown in Figure 6.

In a study of men with borderline hypertension, felodipine and dehydrofelodipine systemic availability increased 2.5- and 1.7-fold, respectively, when felodipine was taken with grapefruit juice relative to water (5). Under the same conditions, plasma levels of nifedipine and dehydronorfedipine increased 1.4- and 1.2-fold. The results with felodipine were reproduced in another study in nine healthy middle-aged men (46). The interaction with grapefruit juice may be due to inhibition of first-pass oxidative metabolism by flavonoids in the grapefruit juice, but the precise mechanism of interaction has not been identified.

Itraconazole systemic availability increased two- to threefold following a standard breakfast compared with during fasting (194). In contrast to itraconazole, absorption of fluconazole was relatively insensitive to food, both C_{max} and AUC being slightly reduced or unchanged by meals. Although these divergent results are consistent with previous data on these agents, there is no mechanistic explanation for their different behavior. In six healthy volunteers, levodopa absolute bioavailability from an immediate release dosage form was

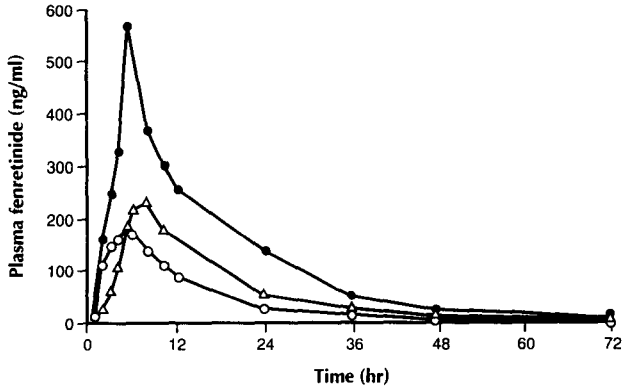

Figure 6 Mean plasma versus time concentrations of fenretinide in 13 subjects following a single 300-mg oral dose of fenretidine administered during fasting (*open circles*) and after a meal (*closed circles*), and as a 20-ml neutral oil suspension administered during fasting (*triangles*). (Reproduced with permission from Reference 39.)

86.4 and 80.4% from fed and fasting treatments, respectively. Levodopa availability from a controlled release dosage form was 71 and 63.6% from fed and fasted treatments, respectively (209). Although the controlled release dosage form yielded lower absolute bioavailability, the food effect was similar for both formulations. A diet rich in insoluble fiber (DRIF) increased levodopa plasma levels by 30% in patients after two weeks on a DRIF diet compared with baseline (3). Thus, the DRIF may serve the useful purpose of relieving constipation, and also of increasing plasma levels and presumably the effectiveness of levodopa.

Peak plasma nifedipine concentrations were increased 1.8- and 2.4-fold by low-fat and high-fat meals, respectively (92). Overall systemical availability was increased 1.2-fold by both treatments. The increased nifedipine plasma levels appeared to be without effect on blood pressure relative to the fasting state, but mean heart rate increased by 10 beats/min after both postprandial doses compared to 5 beats/min during fasting. A dramatic food effect occurred with oral micronized progesterone (175). Repeated doses of micronized progesterone were administered in capsules for 5 days to 15 healthy postmenopausal women, either 2 h before or immediately after a standard breakfast. Peak day 1 and day 5 plasma levels of progesterone were increased fivefold, and systemic availability was increased twofold, by food. Increased progesterone absorption with food was attributed either to a direct drug-food interaction in the GI tract, or to increased blood flow to the liver, causing decreased presystemic clearance.

Similar to observations with cefetamet pivoxil (17, 180), food had a positive effect on the new ester-type oral cephalosporin S-1108 (161). Systemic availability of S-1108 was increased approximately 1.5-fold, and peak plasma levels increased 1.2-fold following a Japanese-style breakfast. Ceruletide diethylamine had no effect on S-1108 absorption, but t_{max} was delayed. Ranitidine had a negative effect. Thus, neither increased bile flow nor increased gastric pH seem to contribute to food-related increase in S-1108 absorption. A dramatic interaction was observed with the piperazine derivative dopamine reuptake inhibitor vanoxerine (82). Administration of 100 mg of vanoxerine to healthy men after low-fat and high-fat breakfasts increased systemic availability 1.8-fold and 3.6-fold, respectively. Despite the considerable increase in systemic availability after the high-fat meal, C_{max} was increased less than twofold because of delayed absorption. One subject who was virtually unaffected by food intake was a poor metabolizer of debrisoquine, which suggested that decreased first-pass metabolism, possibly related to increased splanchnic blood flow, may have contributed to the food effect in the other subjects.

Absorption of the nootropic agent vinpocetine and also the 5-hydroxytryptamine$_{1a}$ partial antagonist zalospirone is modestly increased by food (91, 106). Administration of vinpocetine tablets 10 min before and 10 and 30 min after starting a standard breakfast increased systemic availability 1.6-, 1.7-, and 2.0-fold relative to fasting. Peak plasma levels and areas under plasma curves of zalospirone were increased approximately 1.4-fold by food in both young and elderly subjects (91). Plasma levels were almost doubled in elderly subjects relative to young subjects. The results of these studies led to the recommendation that both vinpocetine and zalospirine be taken with or after meals.

The last drug listed in this category reflects the dramatic positive effect that food can have on circulating drug profiles. Systemic availability of a novel antiprotozoal agent 566C80 was increased 3.3-fold, and C_{max} was increased 5.4-fold, when administered after food (79). In attempts to elucidate the mechanism of this interaction, 566C80 was given during fasting, with meals of varying fat content, as an aqueous suspension, as an oily emulsion, and after an infusion of cholecystokinin octapeptide (CCK-OP) (153). Results from these studies led to the conclusion that increased absorption of 566C80 after food could be quantitatively accounted for by dietary fat.

CASES IN WHICH FOOD HAS NO EFFECT ON DRUG ABSORPTION

The reports summarized in Table 4 describe studies in which food had little or no effect on drug absorption. Some compounds in this table are also cited in Tables 1–3. This reflects the varied results that may be obtained under

Table 4 Drugs whose absorption is not affected by food

Drug	Ref.	Drug	Ref.
Alprazolam	48	Methotrexate	144
Amlodipine	51	Metoprolol succinate	165, 166
Bambuterol	157	Morphine sulfate	11
Bisoprolol and hydrochlorothiazide	123	Mosapride citrate	162
Brofaramine	16	Moxonidine	188, 198
Bromocriptine	94	Nefiracetam	58
Carbamazepine	6	Paroxetine	63
Cardizem	220	Piroximone	66
Cefetamet pivoxil	42	Procainamide	37
Cimetidine and ranitidine	34	Pseudoephedrine and brompheniramine	19
Cyclosporine	74,104	Rifabutin	127
Diazepam, ethinyl estradiol, norethindrone, propranolol	150	Sparfloxacin	163, 187
		Temafloxacin	62, 109
Diazepam	45	Theophylline	2, 69, 146
E2020	120	Tiaprofenic acid	207
Fluvoxamine	193	Trimetazidine	21
Ibuprofen	102	Verapamil	35, 36, 97
Levodopa	151		

different study conditions, from different laboratories, or with different formulations of the same drug.

Alprazolam absorption was essentially unchanged by food when it was administered in a prototype mixed polymeric controlled release tablet formulation. Mean peak circulating drug levels increased 12% with food, but other pharmacokinetic parameters were unchanged (48). Lack of food effect in this case is not surprising as the in vitro dissolution rate for this formulation was pH independent, and in vivo plasma clearance of alprazolam is low so such that metabolism is primarily determined by hepatic metabolic capacity rather than by blood flow.

While absorption of hydrochlorothiazide has previously been reported to be both increased (13) and decreased (7) by food from conventional single-drug formulations, absorption of both hydrochlorothiazide and bisoprolol was unaffected by food when they were administered in a combination tablet (123). No significant differences were observed in plasma pharmacokinetic parameters, nor in the percentage of hydrochlorothiazide excreted in urine.

Ingestion of the selective monoamine oxidase A (MAO-A) inhibitor brofaromine together with cheese containing the equivalent of a 30% protective

a maximum change of only 20 mm Hg in three subjects. The mean increase in blood pressure was only 11 mm Hg compared to 40 mm Hg from an equivalent dose of tyramine. The lack of interaction with tyramine-rich foods may greatly increase the benefit-risk ratio of these MAO-A inhibitors (16). Neither food nor metoclopramide had a significant effect on plasma profiles of bromocriptine (94). Consistent with its effects on gastric emptying, food caused a slight delay in bromocriptine absorption, whereas metoclopramide had the opposite effect. Both changes were trivial.

Although previously cited studies showed increases in absorption of the cephalosporin prodrug cefetamet pivoxil from tablets (17, 180), food had no effect on absorption from an oral syrup formulation. Mean C_{max} values in plasma were 2.7 mg/ml with food compared to 2.9 mg/ml during fasting, and absolute bioavailability was 38 and 34% after fed and fasting doses, respectively. Interestingly, the syrup yielded significantly lower absolute systemic bioavailability compared with a tablet under fed conditions. Absorption of both cimetidine and ranitidine was unaffected when they were administered to healthy male subjects after a meal compared with during fasting (34). In the fasted state, absorption of cimetidine was decreased 24%, and ranitidine was decreased 59%, when these compounds were taken with an antacid. In the fed state, however, coadministered antacid did not have the same effect on cimetidine or ranitidine absorption. It is proposed that the antacid effect seen in the fasting state is related to impaired tablet dissolution after drug binding to unabsorbed antacid. Abolition of this effect by food may be due to competition for drug binding sites on the antacid.

In a study cited in Table 3, bioavailability of cyclosporine from a chocolate emulsion was 23 and 42% after low-fat and high-fat meals, respectively (65). Other studies have reported no significant change (104) or decreased cyclosporine absorption with food (89). Significant increases in cyclosporine absorption with food have been reported in renal transplant patients (148). Two further studies have reported minimal effect of food on cyclosporine absorption (74, 104). Cyclosporine was administered to 14 renal transplant patients immediately following a moderate- or trace-fat breakfast (74). Neither meal had any significant effect on cyclosporine pharmacokinetic parameters. Mean C_{max} values were 410, 346, and 365 ng/ml, and mean AUC values were 2115, 2085, and 2145 ng•h/ml following fasting, moderate-fat, and high-fat treatments at an average cyclosporine dose of 3.51 mg•kg/day. In the second study, conducted with healthy male subjects, a standard light breakfast caused a 17% reduction in mean peak plasma cyclosporine levels but had no effect on areas under plasma profiles, with mean values of 7283 and 7453 ng•h/ml from a 6-mg/kg dose to fasted and fed subjects, respectively (104). Addition of bile salts to the nonfasted treatment caused mean C_{max} values to increase 1.1-fold and overall bioavailability to increase

1.2-fold relative to fasting. These results suggest that bile acid formation is an important determinant of cyclosporine absorption.

Food had no effect on the rate and extent of absorption of the new cholinesterase inhibitor E2020 (120). Following single 2-mg oral doses of E2020 to healthy male volunteers, mean peak plasma E2020 levels of 3.3 and 3.2 ng/ml, and AUC(0–168 h) values of 166.5 and 172.8 ng•h/ml, were obtained under fasting and fed conditions. A report on the lack of food effect on levodopa absorption illustrates, again, the unpredictability of drug-food interactions (61). An earlier report described inhibition of levodopa absorption by high-protein diets (156). Other studies have described reduced levodopa absorption after a standard luncheon (156) and increased absorption from both immediate and controlled release formulations following a light breakfast (209). In a further study of healthy volunteers, a meal containing 30.5 g of protein had no effect on levodopa absorption from a 150-mg solution dose, whereas absorption was reduced by 10%, and peak plasma levodopa levels were reduced by 26%, when the drug was ingested following a meal containing only 10.5 g of protein (151). Poor bioavailability of levodopa following the low-protein meal, relative to the fasting state, suggests that low-protein diets do not increase levodopa absorption, and any beneficial effects of a low-protein diet on levodopa efficacy for Parkinson's disease may be related to reduced competition for transport across the blood-brain barrier rather than to increased systemic availability.

Following a standard high-fat breakfast, peak plasma levels and overall bioavailability of metoprolol from a single 400-mg dose of a new controlled release formulation increased by only a small extent (166). Following a standard high-carbohydrate breakfast, plasma metoprolol levels from a 50-mg dose were unaffected. Thus, it appears that absorption of metoprolol from a controlled release formulation is affected far less by food than from a conventional release formulation (144).

Previous studies using single doses of controlled release morphine have reported increased or unchanged absorption in the presence of food (87, 80). To determine the effect of food on controlled release morphine under clinical dosing conditions, morphine sulfate was administered at a dose of 30 mg every 12 h for seven doses either immediately after or 2 h before ingestion of standard caffeine-free meals (11). Plasma morphine levels during the 12 h following the last dose were similar in fasted and fed treatments. The AUC for fed subjects was 9.8% less than that for fasted subjects. The lack-of-food effect obtained in this repeated dose study was observed by using the same sustained release formulation to that which exhibited increased absorption with food following single doses (80).

Similar to other quinolone antibiotics, absorption of sparfloxacin appears to be essentially unaffected by food. Following single doses to healthy subjects,

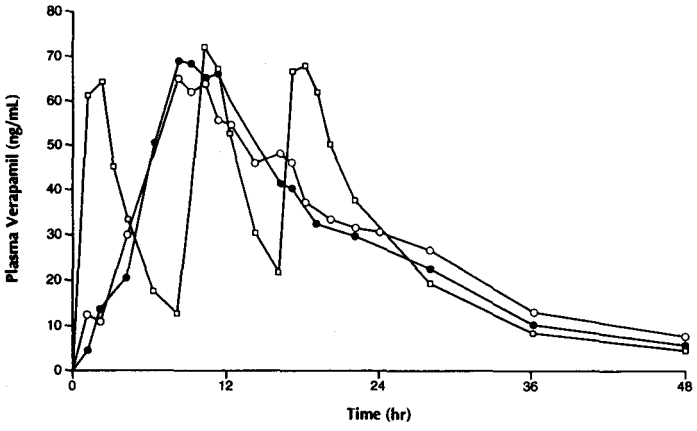

Figure 7 Mean plasma versus time concentrations of verapamil in 12 subjects following once daily oral doses of a 240-mg sustained release verapamil capsule under fasting (*open circles*) and fed (*closed circles*) conditions and after three times daily oral doses of an 80-mg immediate release tablet fasting (*squares*). (Reproduced with permission from Reference 36.)

the time of peak sparfloxacin plasma levels was increased from 3.1 to 4.7 h by food, but peak levels and systemic availability were unaffected (187). In another study, plasma sparfloxacin levels under fed and fasted conditions were almost superimposable (163).

Although food has recently been shown to delay (88, 221) and also to increase (28) absorption of theophylline from controlled release formulations, other studies have shown little effect. The rate and extent of theophylline absorption from Monospan® capsules were almost identical when administered to fasting volunteers or immediately after a high-fat breakfast (69). Similarly, systemic availability of theophylline from Theo-24® capsules was unaffected by enteral liquid feeding in healthy male subjects (146).

The last compound to be discussed in this section is of interest largely because of the divergent food interaction results often reported with controlled release preparations. Verapamil absorption was reduced by 30% and peak serum levels were reduced by 48% when a sustained release tablet was taken with food (76). However, when verapamil was administered in a different sustained-release formulation, there was minimal food effect. Healthy male volunteers received single verapamil doses in a newly marketed sustained-release formulation either during fasting or 10 min after ingestion of a standard breakfast (35, 36). Plasma profiles from the fed and fasting treatments, together with profiles from a conventional 80-mg tablet administered every 8 h, are

shown in Figure 7. Plasma profiles of verapamil following the sustained release capsule were superimposable in the fed and fasting states. Plasma profiles of the metabolite norverapamil were similarly unaffected. The divergent results obtained in these studies are most likely related to the formulations used. Release of drug from membrane controlled-release formulations, including those using osmotic pump technology, are generally less sensitive to the GI environment than other controlled release formulations are. The advantage of a rate controlling membrane dosage form for verapamil was further demonstrated in a study in which the drug was administered as extended release pellets in the fasting state and was also sprinkled on applesauce. How it was administered made no significant difference to plasma verapamil or norverapamil profiles (97).

CONCLUSIONS

The number of articles published during the five years covered by this review illustrates the high level of interest in interactions between drugs and ingested food. As in the initial review on this topic (199), drugs and drug formulations continue to fall naturally into four major categories: those whose absorption is reduced, delayed, increased, or not affected by food. Many of the drugs whose absorption was reduced or increased also exhibited delayed absorption to varying extents. Results of various reported studies have indicated that the nature of a drug-food interaction may be at least partially predictable from a physicochemical perspective, but accurate predictability is plagued by many exceptions, which are often spectacular in nature.

The clinical impact of a drug-food interaction depends on the nature and extent of change in circulating drug levels, the margin of safety, and the slope of the drug concentration-response curve. A small change in circulating drug levels for a drug with a relatively flat dose response curve may be of little clinical consequence. However, a large change in circulating drug levels of a drug with a steep dose response curve, and a narrow safety margin, may have profound clinical consequences.

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