Journal of Pharmacokinetics and Biopharmaceutics, Vol. 5, No. 4, 1977

Influence of Food and Diet on Gastrointestinal Drug Absorption: A Review

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Received Dec. 29, 1976—Final Feb. 17, 1977

The literature concerning the influence of food, and also fluid volumes, on drug absorption is reviewed. In most cases, the absorption of drugs from the gastrointestinal tract is reduced or delayed by food. However, some drugs are unaffected by food, while the absorption of a small number of drugs is increased. Observed effects of food on drug absorption are the net result of various factors, including the influence of food on gastrointestinal physiology and also physicochemical interactions between drugs, drug dosage forms, and dietary components. The intensity of food–drug interactions may be influenced by the type of food and by the time interval between eating and drug administration. Large coadministered fluid volumes tend to promote drug absorption. The clinical significance of changes in drug bioavailability due to these factors is discussed.

KEY WORDS: drug absorption; influence of food; dietary components; fluid volume; clinical significance.

INTRODUCTION

An orally administered drug must be absorbed from the gastrointestinal (GI) tract to an extent and at a rate that will result in circulating drug levels sufficient to elicit a pharmacological response of desired magnitude and duration. The efficiency with which a drug is absorbed is a function of many variables. A drug product has to be sufficiently water soluble to dissolve in gastric and intestinal fluids, or both, and yet for passively absorbed compounds it must be able to diffuse across the lipoidal epithelial lining of the GI tract into the systemic circulation. An acid-labile drug has to be protected so that extensive degradation does not occur in gastric fluids. And a drug that

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irritates the gastrointestinal mucosa has to be formulated so that the irritant effect is prevented or minimized.

The objective of a formulation is to provide a drug product that is stable, attractive, and convenient to use and that has the appropriate physicochemical characteristics for an optimum absorption profile for a particular drug. To achieve, or even approach, this ideal system requires a considerable time and financial investment. Rigid stability and bioavailability criteria that have been set by regulatory agencies must be met before a drug product is accepted for clinical practice. Futhermore, bioavailability studies of a drug product in man are carefully controlled and drugs are administered according to an appropriate experimental design. Volunteers who participate in these studies invariably receive the drugs when they are in a fasting state, so that their blood level and urinary excretion profiles, or both, are obtained free of interference due to food or other agents.

However, there is considerable evidence that drug bioavailability may be influenced by the presence of food in the GI tract, and although information is generally somewhat fragmentary, of some 55 drug products and preparations which appear to have been examined, only four were unaffected by food. Of the remaining 51 products, drug bioavailability was reduced or delayed in some cases and increased in others. It is intriguing to consider that the most sophisticated formulation may be, and frequently is, entirely wasted if the bioavailability of drug from that product is markedly altered by the presence of food.

Although varied drug absorption because of the presence of food may be acceptable for some drugs, it may be critical for agents such as cardiac glycosides, hypotensive agents, anticoagulants, and other drugs that have to be titrated to a patient's condition. It may also be important for antibacterial drugs, particularly bacteriostatic agents whose effectiveness is dependent on maintenance of a minimum inhibitory concentration (MIC) for susceptible organisms in blood or other tissues.

The purpose of this report is to review the literature concerning the influence of food, and specific meal types and dietary components, on the bioavailability of orally dosed drugs in man. However, in order to understand the proposed mechanisms of many reported interactions, it is appropriate first to review some pertinent aspects of GI physiology and the interplay between GI physiology and motility with solid and liquid meals.

GASTROINTESTINAL PHYSIOLOGY

Mechanisms of gastrointestinal drug absorption, methods of studying absorption, and physiological factors influencing the bioavailability of oral dosage forms have recently been reviewed (1,2) and will not be discussed in

this report. Of greater interest here is how food ingestion influences gastrointestinal physiology and how this may, in turn, affect drug absorption. Two physiological functions that are of primary importance are blood flow rate and the regulation of gastric motility and emptying.

Although limited absorption of some compounds occurs via the lymphatic system, the most important absorption route is by direct transfer from the lumen of the GI tract, across the epithelial cell lining, and into the adjacent capillary network leading to the portal circulation. According to Fick's first law, the rate at which a compound diffuses across the capillary membrane (dD/dt) is a function of the concentration gradient across the membrane ($C_{\text{GI lumen}} - C_{\text{blood}}$), and hence of the rate of flow of blood through the capillary. Any changes in the rate of splanchnic blood flow, due to food ingestion, might therefore be expected to have some influence on the absorption efficiency of food components or any other compound available for absorption.

Studies in normal humans have shown that changes in splanchnic blood flow may occur during food ingestion, but the degree of change may vary considerably depending on the type of food (3). After ingestion of a high-protein liquid meal, estimated splanchnic blood flow (ESBF) increased from 1160 ml min^{-1} m^{-2} to 1570 ml min^{-1} m^{-2} during the first hour after feeding. During the next 30 min, the ESBF dropped only slightly to 1430 ml min^{-1} m^{-2}. Following a liquid glucose meal, however, the ESBF dropped from an average of 1065 to 975 ml min^{-1} m^{-2} during the first hour after feeding, and values tended to return to normal during the next 30 min (3). Further studies in man (4) and experimental animals (5) have shown that increased blood flow after eating is not limited to the splanchnic region but occurs also in most other regions of the body and is accompanied by increased cardiac output.

Increased splanchnic blood flow may also influence the absorption of drugs that are extensively metabolized because of changes in the clearance of drug during the first pass through the hepatoportal system. Gibaldi *et al.* (6) and Rowland (7) have described expressions for the degree of hepatic clearance of orally dosed drugs. The fraction (F_L) of an absorbed drug which is available to the general circulation may be expressed in terms of equation 1

$$F_L = 1.0 - Q_{CL,L}/Q_{B,L} \tag{1}$$

where $Q_{CL,L}$ is hepatic clearance of drug, $Q_{B,L}$ is hepatic blood or plasma flow rate, and $Q_{CL,L}/Q_{B,L}$ is the hepatic extraction ratio. It is clear that if $Q_{CL,L}$ is constant and $Q_{B,L}$ increases, then the value of F_L should increase and a greater fraction of an absorbed dose will become available to the circulation. This apparently simple relationship is compounded, however,

by large individual differences in hepatic extraction efficiency and the sensitivity of the extraction ratio to changes in hepatic blood flow rates. Rowland (2) has shown by the use of perfusion models that, for drugs with low extraction ratios, F_L should be relatively insensitive to changes in hepatic blood flow. For drugs with high extraction ratios, however, F_L will be flow rate dependent. Changes in the fraction of drug cleared by the liver may be further complicated by changes in hepatic extraction efficiency due to saturation of metabolizing enzymes when drug is carried to that organ at faster rates.

Food ingestion may also increase intestinal lymph flow. However, although the lymphatics are a major absorption route for large molecules such as cholesterol, proteins, and fatty acids (8), the very slow flow of lymph compared to that of blood makes the lymphatic route of minor importance for most drugs.

The factors controlling gastric motility and gastric emptying have been reviewed by Hunt and Knox (9) and more recently by Bates and Gibaldi (1). It is important to note that most quantitative studies on gastric and intestinal motility have used liquid or semiliquid meals. The influence of solid meals on GI physiology is more difficult to study quantitatively, and this type of information is scarce.

Although absorption of many compounds, particularly those which are soluble and yet un-ionized in gastric fluids, does occur from the stomach, most drugs are optimally absorbed from the small intestine. This is particularly true for weakly basic compounds, which tend to be un-ionized in the relatively high intestinal *p*H, and for compounds absorbed from the small intestine by active carrier mechanisms, but this is a general rule for most compounds because of the large absorptive epithelial surface area of the intestinal mucosa. Any factor which delays stomach emptying has the potential, therefore, of delaying the absorption of an orally dosed drug.

In addition to mechanical mixing, reduction of solid food to semifluid chyme, and proteolytic digestion, a major function of the stomach is to regulate the rate at which its contents are emptied into the duodenum. Early studies with liquid meals suggested that the stomach emptied these liquid test meals into the duodenum in apparent first-order fashion (10). Further analysis of previous data by Hopkins (11) showed that a plot of the square root of the volume of a liquid meal remaining in the stomach vs. time gave a better linear relationship than a logarithmic plot. Some typical results obtained in his analysis are shown in Fig. 1.

Distension of the stomach is the only natural stimulus known to increase gastric emptying, and it was noted by Hopkins that the radius of a cylinder varies with the square root of the volume, and that, by the law of Laplace, the circumferential tension is proportional to the radius. Thus the

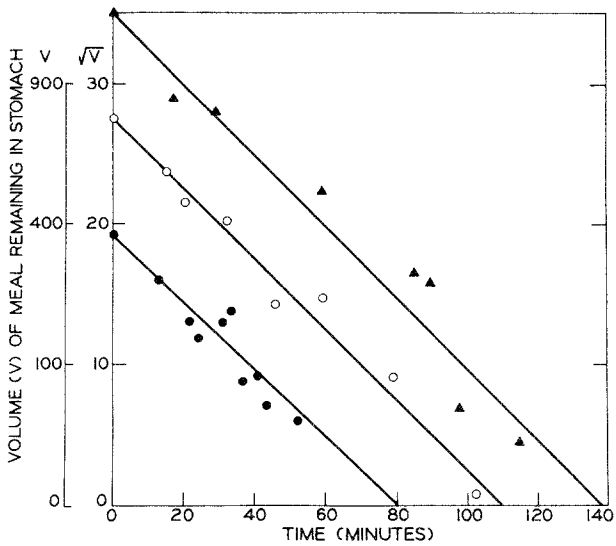

Fig. 1. Square roots of volumes of liquid test meals recovered after various times in human subjects. Reproduced by permission from *J. Physiol. (Lond.)* **152:**144–149 (1966).

observed square root pattern of emptying may be rationalized in terms of varying tension on receptors in the stomach wall (12).

Another factor to be considered is that gastric emptying may be retarded by the activity of receptors situated in the duodenum and small intestine. Three types of receptors have been postulated (9): those responding to osmotic pressure, those responding to acidic molecules with pK_a's less than 5, and those responding to fats or salts of fatty acids. Although the mechanism of action of osmoreceptors has not been clearly defined, it is generally agreed that the higher the osmolarity of a solute entering the duodenum from the stomach, the greater the inhibition of stomach-emptying rate. The acid and fatty acid receptors similarly retard stomach emptying when they are stimulated by entry of low-*p*H or high-fat solutes into the upper small intestine. Thus the various receptors comprise a defense mechanism in preventing injury to the intestinal epithelium.

Gastric emptying may also be delayed by ingestion of hot meals (13), by solutions of high viscosity (14), by fat, and to a lesser extent by protein and carbohydrate (15). Solid diets have been shown to almost double stomach-emptying time compared to liquid meals in rats (16). Although passage of a drug from the stomach into the intestine is thus likely to be mechanically inhibited by the presence of food, prolonged residence in the stomach may have varying effects on drug absorption depending on the drug's solubility

and stability in the acidic gastric juices and the lipophilic character of the dissolved molecule.

Once food has passed from the stomach into the upper small intestine, it has a stimulatory effect on intestinal motility, and this increased motility may accelerate dissolution of solid particles and also decrease the diffusion path of drug molecules to the intestinal mucosa. On the other hand, increased intestinal motility also may increase the rate of transit of compounds through the intestine.

Apart from its influence on splanchnic blood flow and GI motility, food ingestion, particularly of fat, also stimulates the secretion of bile flow. Bile salts are surface active and can increase the dissolution of poorly soluble drugs, and hence promote absorption (17). However, bile salts also have been shown to impede absorption of some compounds because they form insoluble complexes (1).

DRUG–FOOD INTERACTIONS

In addition to the above mechanisms, food may influence drug absorption more directly because of adsorption of drug onto food components, chelation of drug by polyvalent metal ions such as calcium and magnesium (18) or complexation with proteins (19). However, the absorption of tetracycline has been shown to increase in the presence of the neutral fat tripalmitin (8). This effect of tripalmitin appears to be associated with removal of calcium ions. Solid or semisolid food may also act as a mechanical barrier preventing drug movement toward the mucosal surface of the GI tract, and it may also indirectly inhibit drug absorption, depending on the digestive capacity of GI secretions.

DRUG–FLUID INTERACTIONS

One factor which has received little attention is the possible influence that fluid volumes have on the absorption of orally dosed drugs. A commonly accepted notion is that drugs are absorbed more rapidly from concentrated solutions than from dilute solutions (20). However, some studies in experimental animals and in man appear to dispute this. Ferguson (21) studied the toxicity of a variety of substances including organic acids and bases and inorganic compounds following oral doses to rats. Equal doses of compounds were administered in water volumes equivalent to 1.25%, 2.5%, and 5% of body weight. The toxicity of all compounds, expressed in terms of median lethal dose (LD_{50}), increased with increasing dilution. Other studies in rats demonstrated that pharmacological activity of orally dosed sodium pentobarbital at a dose level of 50 mg kg^{-1} increased when the dose

was given in a dilute solution (5 ml per 100 g body weight) over activity when it was given in a concentrated solution (0.5 ml per 100 g body weight); and higher salicylate plasma levels were shown from a dilute (0.8%) solution over those when a concentrated (25%) solution (22) was administered. Martin (23) demonstrated the influence of fluid volume on aspirin absorption in man by showing that the initial absorption rate of this drug was doubled when the volume of water ingested was increased from 75 to 150 ml.

One explanation that was suggested for the increased drug absorption from dilute oral solutions was more rapid stomach emptying, because of the greater volume and relative hypotonicity of the solutions compared to concentrated solutions, with consequent exposure of the solute to a greater intestinal surface area (22). An alternative, or additional, explanation may be found in the observations of Ochsenfahrt and Winne (24), who showed that absorption of both un-ionized and ionized acidic molecules from rat intestinal segments was less from solutions made hypertonic with sodium chloride than from hypotonic solutions. Isotonic solutions gave intermediate values. Typical results are reproduced in Fig. 2. The rate of drug absorption was clearly related to net water flux, which was negative (from blood to perfusing solution) with hypertonic solutions, positive with hypotonic solutions, and zero or slightly positive with isotonic solutions. It can be seen also from the figure that absorption of benzoic acid (pK_a 4.2) is faster at pH 2.2 when the molecule is undissociated than at pH 6.2 when it is essentially completely ionized.

The above observations indicate that the ingestion of solid or liquid meals may influence drug absorption in several ways and that observed variations are the result of a number of physiological as well as physical and chemical interactions. These considerations may be compounded by the condition and age of the patient and whether he is ambulatory or bedridden. The large number of contributing factors may explain, in part, the frequent inconsistencies in reports on the influence of food on drug absorption.

Cases have been reported in the literature of food reducing, delaying, increasing, or having no effect at all on the absorption of different drugs. The majority of studies demonstrate an inhibitory effect. However, there are sufficient examples in each category for them to be considered separately.

The results of various studies of drug–food interactions are summarized in Tables I to V. Although most drugs that have been studied, to the reviewer's knowledge, are included, the drugs presented in the tables are intended to be representative rather than exhaustive. Table I includes drug products whose rate and extent of absorption appear to be inhibited to varying degrees by the presence of food. Drug formulations in Table II differ from those in Table I in that their absorption is delayed somewhat by food

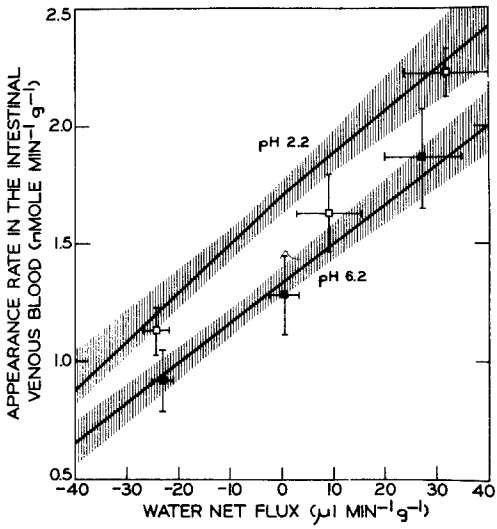

Fig. 2. Dependence of benzoic acid absorption on the water net flux (positive sign: directed toward the blood) in the rat jejunal loop perfused with hypo-, iso-, and hypertonic solutions at *p*H 6.2 and 2.2. The curves with 95% confidence limits (dashed area) were calculated by means of the parameters determined by a kinetic model with the following constants: concentration of benzoic acid in the perfusion solution 16.9 μM, wet tissue weight 0.453 g, perfusion rate 0.11 ml min^{-1}, intestinal blood flow 0.793 ml min^{-1} g^{-1} at *p*H 6.2 and 0.823 ml min^{-1} g^{-1} at *p*H 2.2. Mean values of experimental data with 95% confidence intervals. Reproduced by permission from *Naunyn Schmiedeberg's Arch Pharmacol.* **281**:197–217 (1974).

while the overall absorption efficiency is unaltered. Tables III and IV summarize those studies in which drug absorption is either not affected or is increased by food, while Table V is devoted to studies concerning various erythromycin products.

Because changes in drug absorption characteristics in the presence of food are likely to be influenced by the drug formula, by changes in accompanying water volumes (21–23), as well as by the time interval between eating and dosing, details of whether or not these factors were controlled (or reported) are also included in the tables.

Table I. Drugs Whose Absorption May Be Reduced by Food

Drug	Dosage form	Dosage regimen[a]	Food details	Fluid volume[b]	Time interval[c]	Sampling	Reference
Reduced							
Penicillin G	Tablets	S	Standard breakfast, ?[d]	—[e]	C[f]	Serum levels to 5 hr, urine	(25)
Phenylmercapto-methylpenicillin	Capsules	S	Standard breakfast, ?	—	C	Serum levels to 5 hr, urine	(25)
Penicillin V (K)	Capsules	S	Standard breakfast, ?	—	C	Serum levels to 5 hr, urine	(25)
Pencillin V (K)	Capsules	SM	Standard meal	—	C, varied	Serum levels to 4 hr and during multiple dosing, urine	(26)
Penicillin V (K)	Tablets	S	Standard meal	—	C	Serum levels to 8 hr, urine	(28)
Penicillin V (K)	Tablets	S	Standard meal, ?	—	C	Serum levels to 8 hr, urine	(29)
Penicillin V (Ca)	Tablets	S	Standard meal, ?	—	C	Serum levels to 8 hr	(29)
Penicillin V (acid)	Tablets	S	Standard meal, ?	—	C	Serum levels to 8 hr	(29)
Penicillin V (acid)	Tablets	S	Standard meal	—	C	Serum levels to 8 hr, urine	(28)
Phenethicillin	Capsules and tablets	S	Standard meal	—	C	Serum levels to 5 hr, urine	(25)
Phenethicillin	Tablets	SM	Standard meal	—	C, varied	Serum levels to 4 hr and during multiple dosing, urine	(26,27)
Ampicillin	Capsules	S	Carbohydrate, fat, and protein meals	C	C	Serum levels to 8 hr, urine	(33)
Ampicillin	—	S	—	—	—	Serum levels to 8 hr	(32)
Amoxicillin	Capsules	S	Carbohydrate, fat, and protein meals	C	C	Serum levels to 8 hr, urine	(33)
Pivampicillin	Capsules	S	Standard meal	—	—	Serum levels to 8 hr, urine	(40)
Tetracycline	Capsules	S	Standard meal	C	C	Serum levels to 32 hr	(51)
Tetracycline	—	M	Milk	—	C	Serum level 3 hr after dose	(46)
Tetracycline	Capsules	S	—	—	C	Serum levels to 24 hr	(50)
Demethylchlortetracycline	Capsules	S	Milk	C	C	Serum levels to 120 hr	(47)
Demethylchlortetracycline	Capsules	SM	Food with milk, ?	—	—	Serum levels to 28 hr and during multiple dosing	(49)
Demethylchlortetracycline	Capsules	S	—	—	C	Serum levels to 24 hr	(50)
Methacycline	—	M	Milk	—	C	Serum level 3 hr after dose	(46)
Oxytetracycline	—	M	Milk	—	C	Serum level 3 hr after dose	(46)
Aspirin	—	S	—	—	—	Serum level at 1 hr	(52)
Aspirin (Ca)	Tablets	S	—	—	—	Serum levels to 20 min	(53)
Propantheline	Tablets	S	Standard meal	—	C	Salivary flow rate	(55)
Levodopa	—	M	High- and low-protein diets	—	—	Clinical response	(58)
Rifampicin	—	S	Standard high-fat meal	—	C	Serum levels to 12 hr, urine	(63)
Slightly reduced							
Doxycycline	Capsules	SM	Food with milk, ?	—	—	Serum levels to 28 hr and during multiple dosing	(49)
Doxycycline	Capsules	S	Carbohydrate, fat, and protein meals	C	C	Serum levels to 48 hr	(51)

[a] S, Single dose; M, multiple dose; SM, both single and multiple doses.
[b] Volume of water ingested with the drug.
[c] Time interval between eating and dosing.
[d] Details of meal not given.
[e] Details not given.
[f] Fluid volume or time interval controlled.

DRUGS WHOSE ABSORPTION MAY BE REDUCED BY FOOD

Most of the penicillins for which data are available fall into the category of drugs whose absorption may be reduced by food. Their inclusion in Table I demonstrates, however, the somewhat arbitrary distinction between Tables I and II. The preponderance of evidence suggests that absorption of the penicillins is truly inhibited by food, resulting in lower circulating levels and reduced urinary excretion of antibiotics. Other studies indicate that circulating antibiotic levels tend to be sustained when some penicillins are administered with meals, suggesting that absorption may only be delayed. Further quantitative studies are needed to resolve this question.

McCarthy and Finland (25) studied the absorption of penicillin G, penicillin V, phenethicillin, and phenylmercaptomethyl penicillin, all as the potassium salts, after single doses were given to 16 subjects while in the fasting state and on another occasion 15 min after eating a standard breakfast. Sera were assayed microbiologically using four different organisms and, although the various organisms responded differently to the penicillin analogues, trends in serum profiles were similar. All penicillins yielded somewhat later and lower peak serum antibiotic levels following postprandial doses. Serum levels also tended to be prolonged relative to those in fasted subjects, but areas under serum level curves from 0 to 7 hr after dosing were consistently higher in fasted subjects. Average nonfasted/fasted area ratios based on *Staphylococcus* 209P assay were as follows: penicillin V capsules, 0.88; phenethicillin capsules, 0.74; phenethicillin tablets, 0.67; phenylmercaptomethyl penicillin capsules, 0.73; penicillin G tablets, 0.69. Average nonfasted/fasted 0–5 hr urinary recovery ratios were as follows: pencillin V capsules, 0.75; phenethicillin capsules, 0.74; phenethicillin tablets, 0.79; phenylmercaptomethyl penicillin capsules, 0.98; penicillin G tablets, 0.53.

Reduced absorption of phenethicillin and penicillin V because of the presence of food, after both single and repeated doses, was confirmed by Cronk *et al.* (26,27). Mean serum levels obtained in 45 subjects receiving the penicillins before, with, and following a standard meal are shown in Fig. 3. Lower but somewhat more prolonged serum antibiotic activity because of food is evident for both compounds, although the effect is greater for phenethicillin than for penicillin V. Serum levels were still depressed when doses were given up to 3 hr after eating. Reduced phenethicillin absorption in the presence of food was also observed during multiple-dose studies (27). When the drug was administered at 12-hr intervals to subjects, with each alternate dose administered while the subject was fasting, peak circulating levels after the fasting doses were approximately double those obtained when the drug was dosed after meals.

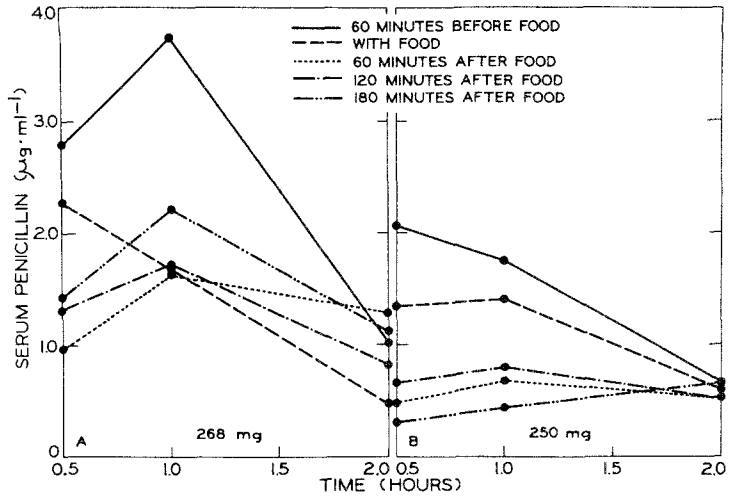

Fig. 3. Effect of food on the absorption of potassium phenethicillin (A) and potassium penicillin V (B). Reproduced by permission from *Am. J. Med. Sci.* **240:**219–225 (1960).

The influence of food on pencillin V absorption was further demonstrated in an excellent study by Berlin and Brante (28). Using healthy nurses as subjects, these authors compared the bioavailability of 150-mg doses of the potassium and calcium salts of penicillin V together with penicillin V acid, all in rapidly disintegrating tablets. Penicillin V acid tablets were formulated from large (100–200 μ) and small (5–10 μ) crystals. Drugs were administered to one group of nurses when they were in a state of fasting and to another group 30 min after a standard breakfast. No differences in bioavailability of penicillin V acid were observed due to particle size. Peak penicillin levels in serum from the acid were reduced from 2 μg ml^{-1} at 1 hr in fasted subjects to 0.8 μg ml^{-1} at 2 hr in nonfasted subjects. Peak serum levels from the calcium salt were similarly reduced from 3 μg ml^{-1} at 0.5 hr to 0.6 μg ml^{-1} at 1 hr, while peak serum levels from the potassium salt were reduced from 4 μg ml^{-1} at 0.5 hr to 0.9 μg ml^{-1} at 1 hr. Thus the findings in this study suggest that the higher serum levels commonly obtained from potassium penicillin V compared to those obtained from penicillin V acid in fasted individuals are not obtained when the drugs are taken with meals. All peak serum penicillin levels were significantly ($P < 0.001$) reduced by food, and the overall serum levels were again prolonged.

About 23% of the dose of penicillin was recovered from the urine of both fasted and nonfasted subjects 8 hr after penicillin V acid had been

administered, suggesting that absorption was not impaired by food. However, the recovery of both salt forms from 8-hr urine was reduced from 33% to 23% when they were ingested after the subjects had eaten. Penicillin V has also been included in Table III because one study indicated that serum pencillin levels from the acid were not affected by food (29). In this study, penicillin serum levels were compared after dosing the acid and the potassium salt to fasting and nonfasting subjects, and peak serum penicillin levels from the potassium salt were again approximately double those from the free acid in fasted subjects. After postprandial doses, however, both drug forms yielded serum levels similar to those obtained from the acid in fasted subjects.

Higher peak serum levels from potassium penicillin V, compared to those obtained from the acid and also the calcium salt, are consistent with more rapid dissolution of the potassium salt in acidic gastric fluids. The relative insensitivity of penicillin V acid absorption to food ingestion may be due to the greater stability of this drug form and to its relatively slow dissolution in the stomach (30).

Inclusion of both ampicillin and amoxicillin in Table I is of particular interest. While it has been established that gastrointestinal absorption of amoxicillin is generally superior to that of ampicillin (31), the relative influences of food on their bioavailability has not until recently been so clearly defined. Neu (32) compared amoxicillin and ampicillin serum levels in 12 individuals in both fasting and nonfasting states. Amoxicillin levels rose more slowly in the presence of food, but peak serum levels were the same as those in fasted subjects. Total areas under serum level curves were not significantly different from the two treatments. On the basis of this study, amoxicillin is included also in Table II. In the same study, serum levels of ampicillin, which are normally one-half those of amoxicillin from equivalent doses, were both delayed and reduced by food.

Contrary to Neu's observations, studies in the reviewer's laboratory (33) in which both ampicillin and amoxicillin were administered to six subjects immediately following various test meals, and also with small and large water volumes to fasted individuals, showed that the absorption of both drugs was significantly reduced by food. Mean serum levels obtained in this study are reproduced in Figs. 4 and 5. It is clear from the figures that serum levels of both agents are considerably reduced when they are administered immediately after eating and that the extent of reduction is independent of dietary components. Serum levels in nonfasted subjects were similar to those obtained by Vitti *et al.* (34) under similar conditions.

Among fasted subjects, serum levels of ampicillin were only slightly affected by fluid volumes, while amoxicillin levels were significantly reduced ($P < 0.05$) when the antibiotic was dosed with 25 ml water compared to

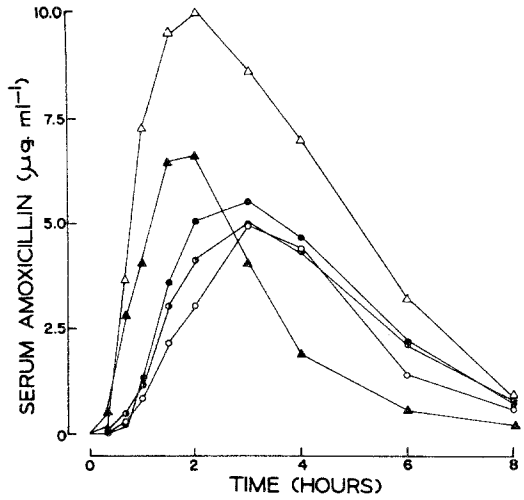

Fig. 4. Average serum levels of amoxicillin in six subjects receiving 500 mg amoxicillin trihydrate in capsules following high-carbohydrate (○), high-fat (●), and high-protein (◑) meals and in the fasted state with 25 ml (▲) and 250 ml (△) of water. Reproduced by permission from *J. Pharm. Sci.* **66**:549–552 (1977).

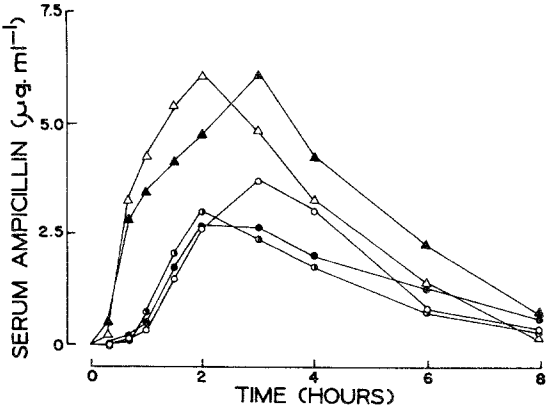

Fig. 5. Average serum levels of ampicillin in six subjects receiving 500 mg ampicillin trihydrate in capsules. The treatment associated with each curve is the same as in Fig. 4. Reproduced by permission from *J. Pharm. Sci.* **66**:549–552 (1977).

250 ml water. The reason for this marked affect on amoxicillin levels is not entirely clear, but possibly it is related to the different water solubilities of the two compounds. The solubility of ampicillin trihydrate in water is 1:90, whereas that of amoxicillin trihydrate is 1:370 (35). Thus a reduction in accompanying fluid volume is likely to reduce the dissolution and absorption of amoxicillin to a greater extent than those of ampicillin. The 8-hr urinary excretion of both amoxicillin and ampicillin was significantly greater in fasted subjects receiving drug with 250 ml water than after all nonfasting treatments.

Pivampicillin is another ampicillin derivative with reported superior bioavailability characteristics compared to ampicillin (36), Pivampicillin is normally given to patients with food to minimize GI irritation, so the influence of food on its bioavailability is important. Several studies have produced conflicting results. Absorption was not affected when pivampicillin was dosed following a light uncooked meal (37), whereas a distinct reduction in serum levels was reported when the drug was administered with a breakfast of eggs and dairy products (38,39). In the study cited in Table I (40), the absorption of pivampicillin (350 mg) was compared in 15 subjects in both the fasting and nonfasting states. Although pivampicillin produced somewhat higher serum levels of antibiotic than ampicillin in fasted subjects, pivampicillin absorption was considerably reduced by a standard cooked breakfast. Mean peak ampicillin levels from pivampicillin doses were reduced from 4.5 to 3.3 $\mu g\ ml^{-1}$ by the presence of food, while the mean total area under the serum level curve was reduced from 15.3 to 8.0 $\mu g\ hr\ ml^{-1}$. Interestingly, the 8-hr urinary recovery of ampicillin after pivampicillin doses was reduced only slightly, from 62% to 55% of the dose in nonfasted individuals.

Interference with both the bioavailability and *in vitro* pharmacological activity of various tetracyclines, due to chelation with heavy metal ions or binding to macromolecules, is well documented (41–45). Although the absorption efficiencies of orally dosed tetracycline, oxytetracycline, methacycline, and doxycycline are reduced to a similar extent by iron salts (41), doxycycline absorption is less affected by milk and other dairy products than is that of other tetracyclines (46,47). This may be due to a lower binding affinity of doxycycline to calcium ions (48). Doxycycline absorption has been shown also to be influenced less by solid diets than has the absorption of tetracycline or demethylchlortetracycline (49–51). The results of studies carried out in our laboratory (51) are summarized in Figs. 6 and 7. In these studies, both doxycycline hyclate and tetracycline hydrochloride were administered both as capsules and as solutions to fasted and nonfasted subjects.

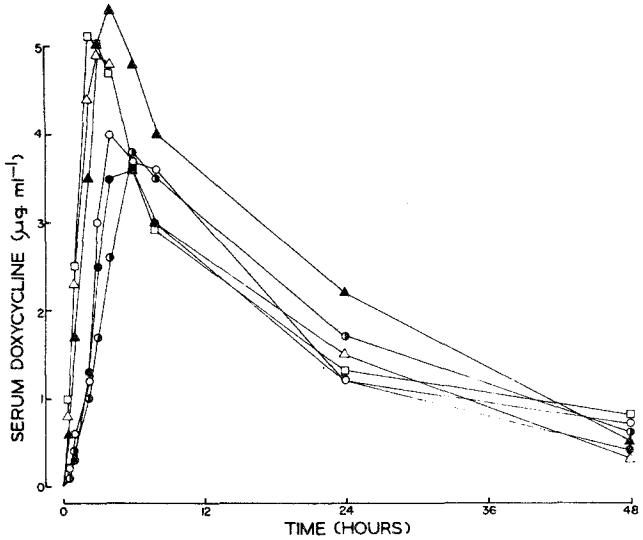

Fig. 6. Average serum levels of doxycycline in six subjects receiving 200 mg doxycycline hyclate in capsules. The treatment associated with each curve is the same as in Fig. 4. Additionally, drug was taken by fasted subjects as a solution in 250 ml water (□). Reproduced by permission from *Antimicrob. Agents Chemother.* **11**:462–469 (1977).

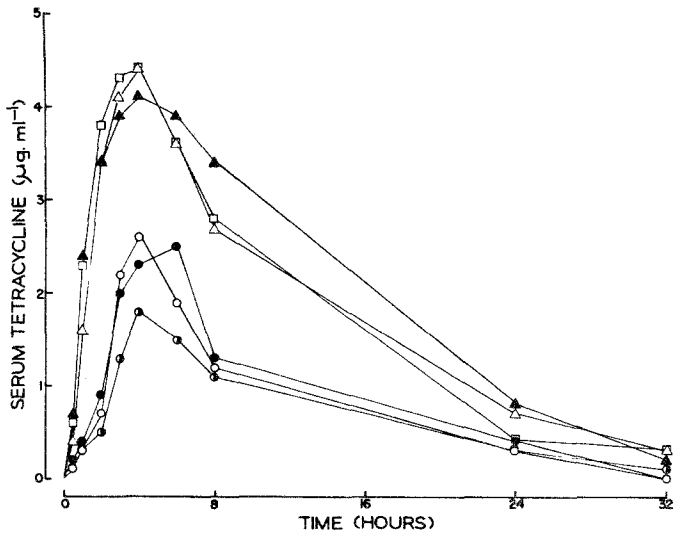

Fig. 7. Average serum levels of tetracycline in six subjects receiving 500 mg tetracycline hydrochloride in capsules. The treatment associated with each curve is the same as in Fig. 6. Reproduced by permission from *Antimicrob. Agents Chemother.* **11**:462–469 (1977).

Serum tetracycline levels were signficantly reduced by high-carbohydrate, -fat, and -protein test meals; however, no differences were observed among the three fasting treatments. Areas under serum level curves from all fasting treatments were significantly greater ($P < 0.05$) than from all nonfasting treatments. Although doxycycline serum levels were also depressed somewhat by the test meals, differences in serum levels between fasting and nonfasting treatments were generally not significant. The close similarity of serum levels from all nonfasted treatments for each drug is consistent with the high water solubility of the salt forms used and shows that absorption of the salts from capsules is largely independent of dissolution rate or fluid volume effects.

Although aspirin is included in Table I, the two studies reporting reduced absorption are largely anecdotal in nature and provide little information (52,53). In one of these studies (52), mean serum salicylate levels obtained 1 hr following a 1.5-g dose of calcium aspirin were significantly reduced from 12.1 mg % in fasted subjects to 5.9 mg % in nonfasted subjects. In the second study (53), serum salicylate levels were obtained up to 20 min following 650-mg doses of commerical aspirin. Serum salicylate levels up to that time in nonfasted subjects were approximately one-half those in fasted subjects. Although this is insufficient time for kinetic interpretation, the authors estimated that the absorption half-time was more than doubled by the nonfasting condition.

The suggestion that serum salicylate levels from dosed aspirin may be both reduced and delayed by food is not readily explained. Aspirin is absorbed from both the stomach and the intestine and is rapidly hydrolyzed to salicylate while it is in the GI tract, during transit across the GI wall, and during its first pass through the liver (54). Salicylate, on the other hand, is not appreciably metabolized in the GI tract or during transit through the gut wall, and it undergoes little or no first-pass effect. Hence any delay in stomach emptying by food should have little effect on the rate of appearance or the height of serum salicylate levels. However, direct interactions between food components and drug may reduce absorption. A more satisfactory understanding of the influence of food on aspirin bioavailability requires detailed studies incorporating blood profiles of both aspirin and salicylate.

The influence of food on the absorption of propantheline was studied by monitoring the anticholinergic effect (reduction of salivary flow rate) in fasted and nonfasted subjects following single oral doses of conventional tablets (55). Single tablets (15 or 30 mg) were taken either after an overnight fast or immediately following a standard breakfast. Typical results obtained in one of three subjects are shown in Fig. 8. The degree of suppression of anticholinergic effect was calculated from differences in areas under

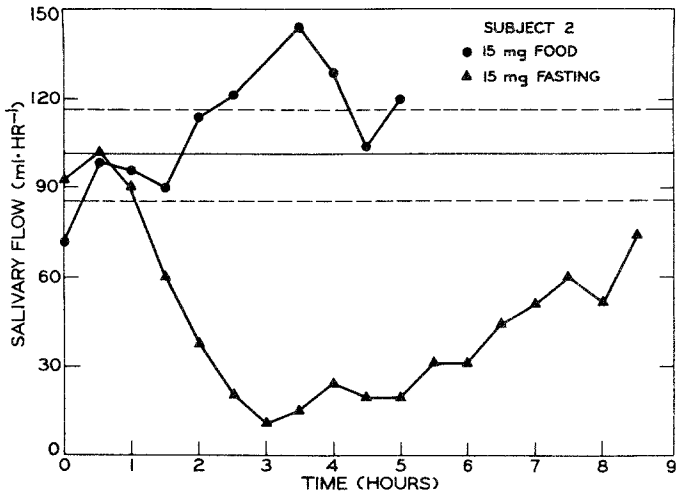

Fig. 8. Effect on salivary flow rate of a 15-mg dose of propantheline ingested after an overnight fast or immediately after a standard breakfast. Reproduced by permission from *Clin. Pharmacol. Ther.* **18:**457–461 (1975).

response–time curves in fasted and nonfasted subjects. For the individual in Fig. 8, the anticholinergic effect of propantheline was abolished after postprandial doses, while in the two other subjects response was reduced by 37% and 62%. These data clearly indicate the need for reevaluation of standard directions for oral propantheline doses to be taken with meals.

Levodopa presents an interesting example of how food components may reduce drug absorption by competitive inhibition at the absorption site. Levodopa is absorbed and transported by the same mechanisms which transport other large, neutral amino acids (56) and might compete with them for absorption as well as penetration into the brain (57). Gillespie *et al.* (58) evaluated the clinical response of eight patients with parkinsonism who were receiving levodopa alone, and also together with the metabolic inhibitor *d,l*-alphamethyldopa hydrazine. Drugs were administered while patients were on controlled diets providing 0.5, 1, and 2 g of protein per kilogram of body weight per day and also 10 g protein per patient per day. All diets were maintained isocaloric by reciprocal variation of carbohydrate content. The results, based on neurological and hormonal effects, clearly showed that the high-protein diets inhibited the therapeutic effect of levodopa. Differences were most marked during administration of levodopa alone without the metabolic inhibitor. Coadministration of *d,l*-alphamethyldopa hydrazine reduces the effect of protein intake by decreasing the required dose of levodopa and inhibiting its metabolism to inactive

compounds. The results obtained in this study support the concept of competitive inhibition of levodopa absorption by dietary amino acids and the need for dietary restrictions in patients receiving this therapy.

Although it is generally recommended that rifampicin be dosed on an empty stomach because food reduces its absorption, evidence from comparative studies is conflicting. There is considerable evidence that rifampicin absorption is delayed by food (59,60), but the delay is not always associated with reduced peak serum levels (61). Rifampicin absorption may be severely limited by food after low (150 mg) drug doses, but it may be decreased, unchanged, or increased after relatively high (700 mg) doses (62).

In a controlled study in 18 patients receiving single 600-mg doses of rifampicin, Siegler *et al.* (63) obtained mean peak serum drug levels of 8.8 $\mu g\,ml^{-1}$ at 2 hr in fasted patients and 6.6 $\mu g\,ml^{-1}$ at 4 hr following a high-fat breakfast. The peak heights in fasted patients were significantly higher ($P < 0.01$) than those from postprandial doses, as were the respective areas under serum level curves of 45.5 and 35.1 $\mu g\,hr\,ml^{-1}$. Twenty-four hour urine accounted for 18.4% of the fasting dose and 13.2% of the postprandial dose ($P < 0.05$). Despite these differences, serum drug levels from both treatments were greater than the MIC for *Mycobacterium tuberculosis* for at least 10 hr after dosing. The authors concluded that the observed changes were of no clinical significance.

DRUGS WHOSE ABSORPTION MAY BE DELAYED BY FOOD

Drugs whose absorption may be delayed by food are listed in Table II. It must be stressed again that separation of drugs into "reduced" and "delayed" categories is somewhat arbitrary in some cases and is based on information currently available. The behavior of particular drugs and drug formulations may need to be redefined as further controlled studies are reported. The inclusion of aspirin effervescent tablets and digoxin elixir in this table, while other dosage forms of these drugs appear in Table I or III, indicates the influence formulation may have on drug–food interactions. The influence of formulation factors will become more apparent during discussions on erythromycin products.

Most of the cephalosporins and sulfonamides which have been studied fall into the delayed category. Harvengt *et al.* (64) compared the absorption of cephradine and cephalexin after oral doses to six fasted subjects, then to the same subjects 30 min after breakfast. After 500-mg doses of cephalexin, peak serum levels of 18.7 ± 1.0 (SD) and 19.8 ± 5.6 $\mu g\,ml^{-1}$ were obtained at 1 hr in fasting and nonfasting states, respectively. After 500-mg doses of cephradine, similar peak serum levels of 18.3 ± 2.0 and 19.2 ± 4.1 $\mu g\,ml^{-1}$ were also obtained at 1 hr. Serum levels of both agents were depressed in

Table II. Drugs Whose Absorption May Be Delayed by Food

Drug	Dosage form	Dosage regimen	Food details	Fluid volume	Time interval	Sampling	References
Amoxicillin	—	S	—	—	—	Serum levels to 8 hr	(32)
Cephalexin	Capsules	S	Breakfast, ?	—	C	Serum levels to 6 hr, urine	(64)
Cephradine	Capsules	S	Breakfast, ?	—	C	Serum levels to 6 hr, urine	(64)
Cephradine	Capsules	S	890-calorie meal, ?	—	C	Serum levels to 8 hr, urine	(65)
Sulfanilamide	Suspension	S	Breakfast, ?	C	—	Blood levels to 36–48 hr, urine	(66)
Sulfadiazine	Suspension	S	Breakfast, ?	C	—	Blood levels to 36–48 hr, urine	(66)
Sulfadiazine (Na)	Solution	S	Breakfast, ?	C	—	Blood levels to 36–48 hr, urine	(66)
Sulfadimethoxine	—	S	—	—	C	Plasma levels to 24 hr, urine	(67)
Sulfamethoxypyridazine	—	S	—	—	C	Plasma levels to 24 hr, urine	(67)
Sulfisoxazole	—	S	—	—	C	Plasma levels to 24 hr, urine	(67)
Sulfasymazine	—	S	—	—	C	Plasma levels to 24 hr, urine	(67)
Aspirin	Effervescent tablets	S	Light meal	—	C	Plasma levels to 75 min	(68)
Acetaminophen	Tablets	S	Carbohydrate meal	—	C	Urine	(70)
Digoxin	Tablets	S	Breakfast, ?	—	C	Serum levels to 3 hr, urine	(71)
Furosemide	Tablets and solution	S	Standard breakfast, ?	—	C	Serum levels to 4 hr, urine	(74)
Potassium ion	Tablets and solution	M	Breakfast, ?	—	C	Urine	(75)

nonfasted individuals only at 30 min after dosing. Between 88% and 96% of both drugs was recovered in 24-hr urine after both treatments. The almost identical pharmacokinetic behavior of the two cephalosporins is not surprising considering the close similarity of their molecular structures. In a subsequent study, cephradine absorption was compared in fasted subjects and again in the same subjects when the drug was dosed immediately following an 890-calorie meal (65). In this study, food again had no significant effect on urinary excretion of antibiotic or the total area under the serum level curve. The shape of the serum–drug profile, however, was markedly reduced and delayed. The mean serum levels obtained in both of these subject populations are reproduced in Fig. 9. The differences in the results obtained in the two cephradine studies appear to be due to the different times that were allowed between eating and dosing. However, details of test diets and accompanying fluid volumes were not described in either study, and these also could have contributed to the differences.

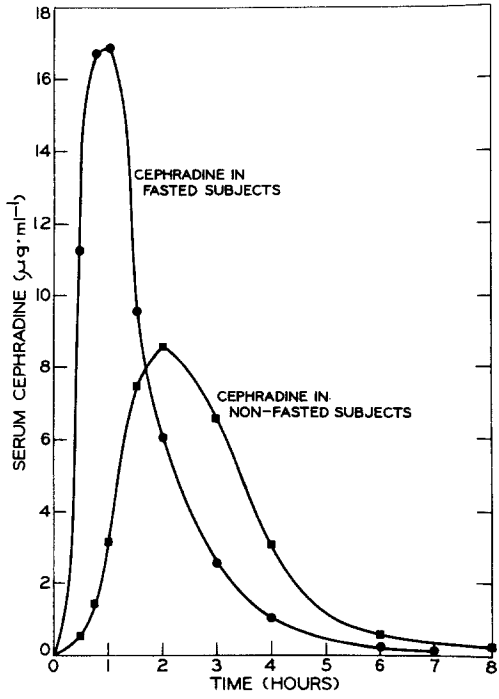

Fig. 9. Serum concentrations after oral cephradine (500 mg) given to fasting and nonfasting subjects. Reproduced by permission from *J. Clin. Pharmacol.* **14**:604–411 (1974).

Both cited studies indicate that sulfonamide absorption is generally delayed by food (66,67). However, changes in absorption efficiency are both compound and dosage-form dependent. Peak serum levels of sulfanilamide from a 5-g oral suspension were reduced only slightly from 10 to 8 mg%, times of peak levels were increased from 30 min to 3 hr, but 72-hr urinary excretion was unchanged when the drug was taken after a meal (66). Sulfadiazine peak serum levels from a similar dose were also delayed, but the actual peak levels increased from 5.5 to 8.7 mg % and 72-hr urinary excretion of drug was increased by food. Serum levels resulting from an oral dose of sulfadiazine sodium solution, on the other hand, were both delayed and decreased by food. Serum levels of the four sulfonamides sulfasymazine, sulfamethoxypyridazine, sulfadimethoxine, and sulfisoxazole were delayed but not reduced when taken after meals (67), with significant differences in serum levels between fasting and nonfasting treatments occurring mainly during the first 1–3 hr after dosing. Urinary recovery of all four compounds was unaffected by food.

The somewhat more prolonged serum sulfonamide levels due to food ingestion suggest that clinical advantages may be obtained by administering these agents with meals, particularly the rapidly eliminated derivatives such as sulfadiazine and sulfisoxazole.

Although absorption of aspirin from conventional tablets appears to be reduced by food (52,53), absorption from effervescent tablets is only slightly delayed, with serum levels from fasted and nonfasted subjects approaching similar values within 30 min of dosing (68). The effervescent preparation may reduce the effect of food by increasing the gastric *p*H. This would decrease the gastric emptying time (69) and would also prevent precipitation of aspirin particles in the stomach.

The study by Jaffe *et al.* (70) probably represents the first controlled study on interactions between a drug and specific dietary components affecting drug absorption. These authors used urinary excretion data to compare the influence of high-protein, high-carbohydrate, and balanced meals on the absorption of acetaminophen in normal individuals. The results obtained from 325-mg doses of acetaminophen in fasted subjects, and also following balanced and high-carbohydrate meals, are shown in Fig. 10. The acetaminophen excretion rate was significantly lower ($P < 0.05$) following the carbohydrate meal compared to other treatments at 1.5 and 3 hr, and was significantly higher following the high-carbohydrate meal at 4.5 and 6 hr. Comparison of urinary excretion data obtained with different carbohydrate meals led to the conclusion that the delay in drug absorption was associated with high pectin content of certain meals. Pectin acts as an adsorbent and protectant in the GI tract and may delay drug absorption by adsorption, complexation, or increase in the viscosity of GI contents.

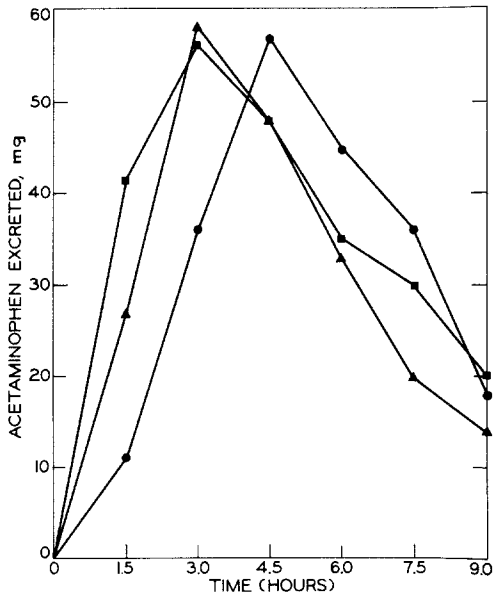

Fig. 10. Mean amount of acetaminophen excreted in the urine during each time interval for fasting (■), balanced (▲), and carbohydrate (●) conditions in five subjects. Reproduced by permission from *J. Pharm. Sci.* **60:**1646–1650 (1971).

Urinary excretion and serum level data were used to compare digoxin absorption from tablets (71,72) and from an elixir (72) (Table III) in fasted and fed individuals. With both types of formulation, cumulative urinary excretion of drug was unaffected by food. No differences were observed in digoxin serum levels at any sampling time in fasted and nonfasted subjects receiving the elixir. Serum levels from the tablet dosage forms were depressed in nonfasted subjects during the first 2–3 hr after dosing but not at later times. Areas under 0–8 hr serum level curves were not significantly different ($P > 0.1$) between fasted and nonfasted doses.

Although these studies indicated little influence by food on digoxin absorption, there was considerable individual variation in the results, with digoxin bioavailability increasing after postprandial doses in some cases and decreasing in others (72). The type of scatter in observed area under serum level curves is indicated in Fig. 11. The results obtained in these single-dose studies confirm earlier observations by White *et al.* (73), who obtained similar mean steady-state plasma digoxin levels in 21 patients receiving the drug either in the fasting state or after breakfast.

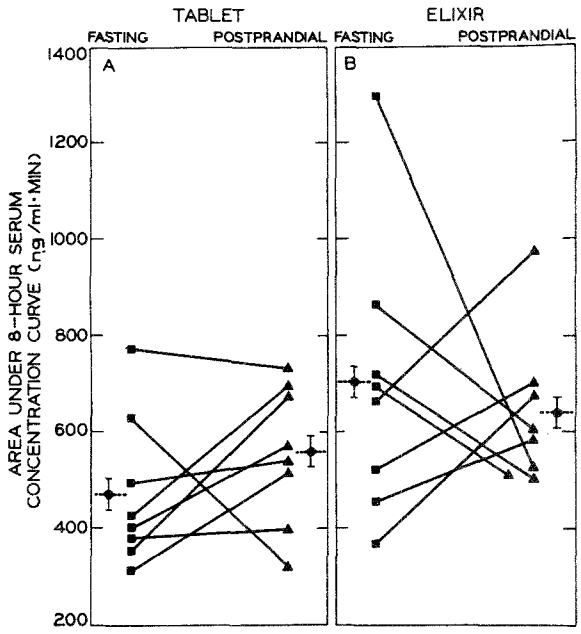

Fig. 11. Area under the 8-hr serum concentration curve after 0.75 mg of digoxin tablets (A) or elixir (B) taken in the fasting and postprandial states. Individual values and means (±SEM) for all subjects are shown. Reproduced by permission from *Clin. Pharmacol. Ther.* **16**:444–448 (1974).

Delayed absorption due to food also has been reported for the diuretic agent furosemide (74) and for potassium ion (75), which may be required as a supplement in chronic diuretic therapy. Serum furosemide levels from tablets and a solution, both of which were dosed orally, were reduced in eight normal individuals when the drug was taken after breakfast compared to levels obtained in the fasting state. In fasted subjects, a mean peak drug level of 2.2 $\mu g\,ml^{-1}$ was obtained 1 hr after dosing. In nonfasted subjects, the mean peak level was reduced to 1.0 $\mu g\,ml^{-1}$ but this level was maintained up to 4 hr after dosing. In two subjects, the 24-hr urinary excretion of furosemide accounted for 50% and 32% of the dose administered in the fasting state and 53% and 37% of postprandial doses. Despite the somewhat depressed serum levels of furosemide in nonfasted subjects, no differences in saluretic response were observed between treatments.

After rapid intravenous doses in this study, furosemide was shown to obey two-compartment model kinetics but nevertheless appeared to have poor distribution capability. The mean volume of the central compartment

was 3.8 liters while the total distribution volume was 5.0 liters. However, these values are based on serum levels of total drug of which only 5% is unbound to plasma proteins (76) and therefore free to diffuse to extravascular sites. Thus the true distribution volumes of furosemide are probably considerably greater than the above calculated values.

The bioavailability of potassium ion from a solution and from slow-release tablets was examined in five individuals in the fasting and nonfasting states (75). Both dosage forms provided 40 mEq of potassium. Bioavailability was calculated from urinary excretion, and there was a significant decrease in 5-hr urinary excretion of potassium from both dosage forms in nonfasted subjects. For the solution, 5-hr urinary excretion values were 31 ± 2.4 mEq and 14.5 ± 3.4 mEq in fasting and nonfasting subjects ($P < 0.01$). The respective values from slow-release tablets were 26 ± 3.3 mEq and 7.8 ± 2.5 mEq ($P < 0.01$). Despite this large reduction in 5-hr urinary recovery due to food, recovery during the 5–8 hr period was greater from both dosage forms in nonfasted subjects, suggesting that potassium absorption had been delayed rather than reduced.

The above results suggest that slow absorption and consequent slow elimination of potassium following postprandial doses should produce less fluctuation in total body stores of potassium than when the drug is dosed on an empty stomach. Since the object of potassium therapy is to replenish and maintain body stores at a desired level, better therapeutic results may be obtained when the drug is administered with food.

There appears to be no information available on the influence of food on barbiturate absorption in man. However, studies in rats have shown that the absorption of both phenobarbital (77) and amobarbital (78) is delayed by the presence of food. In both cases, delayed absorption appeared to be due to increased gastric emptying time. Once the drugs had passed into the small intestine, absorption was rapid, so the extent of absorption was not decreased in nonfasted animals. In this respect, it is interesting to note the observations of Orr and Benet (79) that prolonged fasting of rats for periods greater than 96 hr can lead to marked impairment of drug absorption. This is believed to be because of inhibition of intestinal epithelial cell proliferation due to fasting that leads to reduced viability of mucosal cells and a reduced total absorptive surface area.

DRUGS WHOSE ABSORPTION MAY BE UNAFFECTED BY FOOD

Very few drugs fall into the category of drugs whose absorption may be unaffected by food. Those for which data are available are listed in Table III.

Table III. Drugs Whose Absorption May Be Unaffected by Food

Drug	Dosage form	Dosage regimen	Food details	Fluid volume	Time interval	Sampling	Reference
Penicillin V (acid)	Tablets	S	Standard meal	—	C	Serum levels to 8 hr	(29)
Digoxin	Elixir	S	Standard meal	C	C	Serum levels to 8hr, urine	(72)
Theophylline	Tablets	S	Carbohydrate, fat, and protein meals	C	C	Serum levels to 12 hr	(80)
Prednisone	Tablets	S	Standard meal	C	C	Plasma levels to 24 hr	(83)

Penicillin V acid (29) and digoxin (72) have already been discussed. The bioavailability of theophylline was examined in six normal individuals in six different treatments (80). The study design was similar to those described earlier for ampicillin (33) and tetracycline (51). Three treatments to non-fasted subjects consisted of dosing the drug in tablet form immediately after high-carbohydrate, -fat, or -protein meals. Three treatments to fasted subjects consisted of dosing the drug after overnight fasting with 20 or 500 ml of water, and as a solution. Serum theophylline profiles from all treatments are shown in Fig. 12.

Although theophylline has been shown to obey two-compartment model kinetics after intravenous injection (81), the serum levels following oral doses were best described by equation 2, which is appropriate to the one-compartment open model:

$$C = \frac{FD}{V}\left(\frac{k_a}{k_a - k_{el}}\right)\left[e^{-k_{el}(t-t_0)} - e^{-k_a(t-t_0)}\right] \qquad (2)$$

where C is the concentration of theophylline in serum at any time t after dosing, F is the fraction of the dose D absorbed, V is the distribution volume, k_a and k_{el} are first-order rate constants for drug absorption and drug elimination, respectively, and t_0 is the lag time between dosing and the appearance of drug in serum.

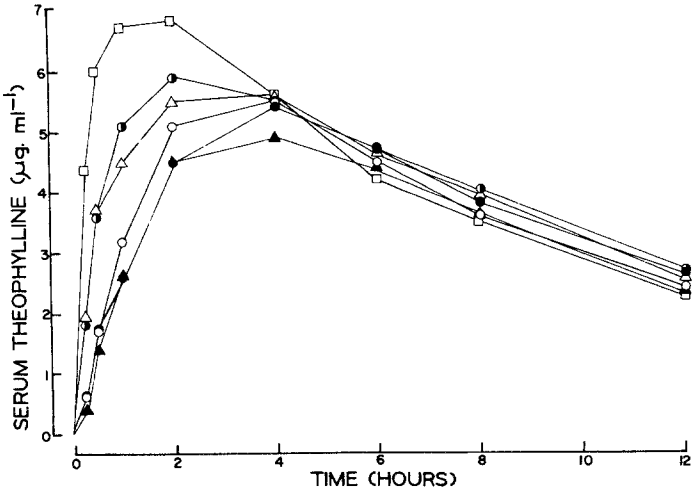

Fig. 12. Average serum levels of theophylline in six subjects receiving 260 mg theophylline in tablets following high-carbohydrate (○), high-fat (●), and high-protein (◑) meals, in the fasted state with 20 ml (▲) and 500 ml (△) of water, and in solution (□). Reproduced by permission from *Clin. Pharmacol. Ther.* **17**:475–480 (1975).

From Fig. 12, it can be seen that no trends were obtained due to treatments, with the exception of the solution dose. Serum levels from the solution were significantly greater than those from all other treatments during 2 hr after dosing ($P < 0.05$). Among other treatments, dosing theophylline immediately after the high-protein meal tended to produce somewhat elevated serum levels. Lowest levels were obtained when the drug was given with a small volume (20 ml) of water on an empty stomach, although differences between these serum levels and those from other tablet doses generally were not significant.

Among the pharmacokinetic parameters, k_a was significantly greater following the solution ($2.9 \pm 0.4\ hr^{-1}$) than from all other doses, and was significantly greater following the protein meal ($1.3 \pm 0.5\ hr^{-1}$) than from other nonfasted treatments. Areas under serum level curves from 0 to 4 hr and from 0 to 12 hr were generally greater following the solution, 500 ml fasting, and the high-protein meal treatment than from the other treatments. However, there were no significant differences in total areas (FD/Vk_{el}) or FD/V values between the treatments. Thus, although food appears to have little effect on theophylline bioavailability, absorption is influenced by the volume of coadministered water. This is not unexpected considering the low solubility of theophylline in aqueous solvents over a wide range of *p*H values.

Prednisone is known to be susceptible to bioavailability problems (82). However, a recent study by Tembo *et al.* (83) showed that food may have little or no effect on its absorption from the GI tract. Prednisone tablets with both fast and slow *in vitro* dissolution characteristics were administered to four male volunteers in the fasted state, then again following a standard breakfast. Plasma levels of prednisolone were determined by radioimmunoassay up to 24 hr after dosing. Analysis of variance and Tukey's multiple comparison test (84) showed no differences between fasted and nonfasted treatments in plasma levels at each sampling time, peak plasma levels, times of peak levels, and areas under plasma level curves to 12 and 24 hr after dosing. The rapidly dissolving tablets produced higher ($P < 0.05$) plasma levels than the slowly dissolving tablets between 1 and 2 hr after dosing, but not at any other time in both fasted and nonfasted individuals.

DRUGS WHOSE ABSORPTION MAY BE INCREASED BY FOOD

Drugs whose absorption may be increased by food are listed in Table IV. The mechanisms causing increased absorption of these drugs have been rationalized, but not proven, in most cases.

Considerable interest has been shown in factors influencing the absorption of griseofulvin due to the very low water solubility and hence poor

bioavailability of this agent. Absorption of griseofulvin has been shown to be increased by high-fat meals but not by high-protein or -carbohydrate meals in normal individuals (85). Absorption is also delayed somewhat by fat, presumably because of delayed stomach emptying, and the ability of fatty meals to promote absorption appears to be time dependent (86). Ingestion of drug immediately following a high-fat breakfast resulted in increased absorption, indicated by an increase in urinary excretion of the major metabolite desmethyl griseofulvin, whereas a high-fat evening meal had little effect. The different influences of the morning and evening high-fat meals on griseofulvin absorption may have been due to reduced motor activity of subjects following the evening meal, although a circadian rhythm effect cannot be discounted.

As griseofulvin is an extremely lipophilic molecule, its dissolution in the GI tract, and hence its absorption, may be accelerated directly by the presence of fat. Dissolution may also be increased indirectly by fat stimulating the flow of bile, containing solubilizing and emulsifying agents, into the duodenum (87,88).

Increased absorption of nitrofurantoin in the presence of food has been rationalized in terms of delayed stomach emptying, permitting more drug to dissolve in the stomach before it passes into the optimal absorption environment of the small intestine (89). Bioavailability of this drug from both microcrystalline and macrocrystalline formulations was increased ($P < 0.01$), although the initial absorption rate from the macrocrystalline formulations was reduced ($P < 0.05$) compared to the fasted state when the drug was taken immediately following a standard breakfast. It is fortuitous that administration of nitrofurantoin with meals in order to avoid GI irritation tends to promote rather than inhibit absorption. A similar situation exists with doxycycline (49–51).

The absorption of propoxyphene was delayed slightly by the presence of food, but overall absorption efficiency was similar in fasted and nonfasted subjects, with plasma levels of drug tending to be higher following postprandial doses (90). When 130 mg propoxyphene hydrochloride was dosed immediately following a high-carbohydrate meal to six subjects, the mean peak serum level of unchanged drug was 161 ± 46 ng ml^{-1}, which was significantly greater ($P < 0.05$) than the peak level obtained following a high-protein meal (118 ± 37 ng ml^{-1}) and almost double those obtained in fasted subjects receiving the drug in capsules or in solution. Absorption was slightly delayed in nonfasted subjects, resulting in reduced serum levels during the first 0.5–1 hr after dosing. Contrary to results reported previously (91), dosing propoxyphene in solution did not result in higher circulating levels of drug than when propoxyphene was dosed in capsule form to fasted subjects.

Table IV. Drugs Whose Absorption May Be increased by Food

Drug	Dosage form	Dosage regimen	Food details	Fluid volume	Time interval	Sampling	References
Increased							
Griseofulvin	—	SM	Carbohydrate ?, fat, and protein? meal	—	—	Serum levels to 8 hr and during multiple dosing	(85)
Griseofulvin	—	M	—	—	C	Urine	(86)
Nitrofurantoin							
Macrocrystalline	Capsules	S	Standard meal	C	C	Urine	(89)
Microcrystalline	Tablets	S	Standard meal	C	C	Urine	(89)
Propoxyphene	Capsules	S	Carbohydrate, fat, and protein meals	C	C	Plasma levels to 24 hr	(90)
Riboflavin	Solution	S	Standard meal	C	C	Urine	(92)
Riboflavin-5′-phosphate	Solution	S	Standard meal	C	C	Urine	(93)
Lithium citrate	Tablets	S	Standard meal	—	C	Urine	(94)
Slightly increased							
Hetacillin	Capsules	S	Standard meal	C	C	Serum levels to 8 hr, urine	

The reason for slightly delayed but increased propoxyphene absorption in the presence of food is not known, but the argument used to explain increased nitrofurantoin absorption may apply (89). This argument is perhaps more pertinent for propoxyphene, as prolonged residence in gastric fluids because of food should promote dissolution of the basic propoxyphene molecule to a greater extent than that of the weakly acidic nitrofurantoin.

Increased absorption of riboflavin (92) and riboflavin-5′-phosphate (FMN) (93) in the presence of food, particularly after high drug doses, has been shown to be consistent with a site-specific saturable absorption mechanism. Urinary recovery of riboflavin following 10-, 20-, and 30-mg doses of both riboflavin and FMN in fasted and nonfasted individuals is shown in Fig. 13. Although absorption of both drug forms was inhibited with increasing doses to fasted subjects, no such inhibition was observed when doses were administered immediately following a standard meal.

These and other results provided unequivocal evidence that both riboflavin and FMN are absorbed by similar mechanisms at a site high in the intestinal tract. In fasted subjects, high doses of vitamin saturated the absorption mechanism, resulting in reduced absorption efficiency. If the vitamin was taken with food, the reduced gastric emptying rate decreased the rate at which drug passed the active absorption sites in the proximal small intestine and facilitated complete absorption over a wide dose range. Construction of Lineweaver–Burk type plots of reciprocals of riboflavin excretion vs. reciprocal of dose differentiated subjects as "high" and "low"

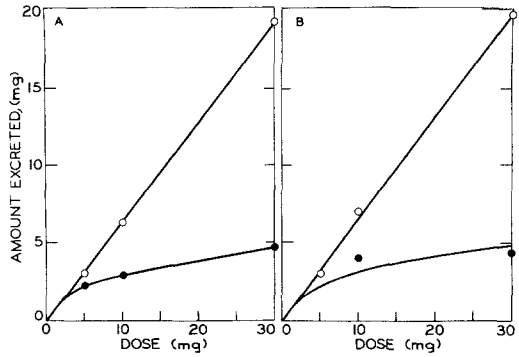

Fig. 13. Urinary recovery of riboflavin after administration of riboflavin (A) and FMN (B) as a function of dose when given on an empty stomach (●) and after a standard breakfast (○). Each point is the mean of four subjects. The two data points for the 5-mg dose in (B) are superimposed. Reproduced by permission from *J. Pharm. Sci.* **55:**285–289 (1966) and *J. Pharm. Sci.* **56:**58–62 (1967).

excretors of riboflavin and confirmed a limited capacity for riboflavin absorption.

Reduced absorption of lithium in fasted, compared to nonfasted, subjects appears to be caused by the purgative effect of lithium ion on the unprotected GI tract (94). Mean 5-day urinary excretion of lithium in ten fasted male subjects receiving 24 mmol lithium citrate in slow-release tablets accounted for $79.2 \pm 3.4\%$ of the dose. When the same dose was given immediately after eating, the urinary recovery was increased to $91.8 \pm 2.4\%$ ($P < 0.001$). The reduction in urinary recovery in the absence of food was clearly associated with a greater incidence of diarrhea in fasted subjects. Fasted subjects who did not suffer from diarrhea absorbed lithium to the same extent as did nonfasted individuals.

Although the absorption of ampicillin and amoxicillin (31–33), and to a lesser extent pivampicillin (40), is reduced by food, the ampicillin precursor hetacillin is absorbed somewhat better when dosed with meals. Jusko and Lewis (95) calculated the absolute bioavailability of orally dosed hetacillin in fasted and nonfasted subjects by comparing areas under plasma level curves and urinary recoveries with those obtained after bolus intravenous doses. Fractional absorptions based on plasma areas (F_A) and urinary excretion (F_u) were calculated by equations 3 and 4, respectively:

$$F_A = \frac{\text{area}_{\text{p.o.}} \cdot \text{dose}_{\text{i.v.}}}{\text{area}_{\text{i.v.}} \cdot \text{dose}_{\text{p.o.}}} \tag{3}$$

$$F_u = \frac{\text{percent recovery}_{\text{p.o.}}}{\text{percent recovery}_{\text{i.v.}}} \tag{4}$$

In four fasting subjects receiving 483 mg ampicillin equivalents of hetacillin, F_A and F_u were 0.36 ± 0.07 and 0.40 ± 0.07, respectively. In the same subjects receiving hetacillin immediately following a standard breakfast, F_A and F_u were 0.42 ± 0.10 and 0.43 ± 0.16. Although differences between relative fasting and nonfasting values in this small number of subjects were not significant, the results are consistent with observations of Sutherland and Robinson (96) that 6-hour urinary recovery of ampicillin after a 500-mg dose of hetacillin increased from 32% in fasted subjects to 48% in nonfasted subjects.

ERYTHROMYCIN

Since the introduction of erythromycin in 1952 (97), and subsequent observations that the drug is irregularly absorbed from the GI tract (98), a large number of derivatives and formulations have been prepared in an attempt to optimize its stability and absorption characteristics.

Reports on erythromycin absorption from various dosage forms in the absence and presence of food are often conflicting. Results of reported studies are given in Table V. The absorption of erythromycin base has been reported to be reduced, delayed, or not affected by food, depending on the formulation or dosage regimen used. Josselyn and Sylvester (98) studied the absorption of erythromycin from plain and coated tablets administered before or after a meal. Postprandial dosing to subjects caused a marked decrease in erythromycin blood levels from the plain tablet. With coated tablets, however, acid degradation of erythromycin in the stomach was decreased, and, apart from a slight delay in absorption, food had little influence on erythromycin blood levels from this dosage form. Acid degradation of erythromycin in plain tablets was reduced by dosing the subjects with aluminum hydroxide, but not by dosing with sodium citrate. Similar results were obtained when erythromycin was administered in gelatin capsules and coated tablets (99). Serum erythromycin levels from capsules were reduced when doses were given 1 hr after breakfast, while serum levels from coated tablets were only delayed. It is interesting that patients with pernicious anemia, with little or no gastric secretion of acid, absorbed erythromycin equally as well when capsules were dosed before or after meals.

More recent multiple-dose studies in male subjects have shown that the absorption of erythromycin from an enteric coated tablet is unaffected by food and that serum levels from enteric coated tablets of erythromycin may be 2–4 times higher than levels obtained from equivalent postprandial doses of erythromycin stearate in film-coated tablets (100).

Reduced bioavailability of erythromycin stearate from coated tablets in the presence of food has been confirmed in single- and multiple-dose studies. Hirsch and Finland (101) compared the effect of food on the absorption of erythromycin stearate (coated tablets), erythromycin estolate (capsules), and triacetyloleandomycin (capsules) in adult subjects. Serum antibiotic levels from both the estolate and the stearate were markedly reduced by food. Triacetyloleandomycin levels, on the other hand, were hardly affected apart from a slight delay in absorption. Similar results were obtained by Clapper *et al.* (102) in a crossover study of erythromycin stearate (coated tablets) and erythromycin estolate (capsules) in ten subjects. Mean peak serum antibiotic levels following single doses equivalent to 250 mg erythromycin base were 0.29 ± 0.17 and $0.17 \pm 0.33\ \mu g\ ml^{-1}$ in fasting and nonfasting subjects receiving erythromycin stearate. Relative values from the estolate were 0.78 ± 1.2 and $0.30 \pm 0.36\ \mu g\ ml^{-1}$. Although peak levels appear to be considerably reduced by food, differences between fasted and nonfasted values were not significant ($P > 0.1$) because of considerable variation in individual serum levels. Mean peak serum values were obtained at 2 hr after dosing for all four treatments.

Table V. Influence of Food on the Absorption of Erythromycin Products

Drug	Dosage form	Dosage regimen	Food details	Fluid volume	Time interval	Sampling	Observed effect on absorption	Reference
Erythromycin	Capsules	S	Breakfast, ?	—	C	Serum levels to 6 hr	Reduced [a]	(99)
Erythromycin	Coated tablets	S	Breakfast, ?	—	C	Serum levels to 6 hr	Delayed	(99)
Erythromycin	Tablets	S	—	—	—	Blood levels to 8 hr	Reduced	(98)
Erythromycin	Coated tablets	S	—	—	—	Blood levels to 8 hr	Delayed	(98)
Erythromycin	Coated tablets	SM	—	C	C	Serum levels to 6 hr and during multiple dosing	Unaffected	(100)
Erythromycin stearate	Suspension	S	—	—	—	Blood levels to 6 hr	Unaffected	(105)
Erythromycin stearate	—	SM	Standard meal	—	C	Serum levels to 6 hr and during multiple dosing	Reduced	(104)
Erythromycin stearate	Coated tablets	S	—	—	—	Serum levels to 8 hr	Reduced	(102)
Erythromycin stearate	Coated tablets	S	—	—	—	Serum levels to 25 hr	Reduced	(101)
Erythromycin stearate	Coated tablets	S	Carbohydrate, fat, and protein meals	C	C	Serum levels to 12 hr	Reduced	(103)
Erythromycin estolate	Suspension	S	Standard meal	C	—	Serum levels to 8 hr	Unaffected	(106)
Erythromycin estolate	Suspension	S	Breakfast, ?	C	C	Serum levels to 12 hr	Unaffected	(107)
Erythromycin estolate	—	SM	Breakfast, ?	—	C	Serum levels to 6 hr and during multiple dosing	Unaffected	(104)
Erythromycin estolate	Capsules	S	—	—	—	Serum levels to 8 hr	Reduced	(102)
Erythromycin estolate	Capsules	S	—	—	C	Serum levels to 25 hr	Reduced	(101)
Erythromycin ethyl carbonate	Suspension	S	Standard meal	C	—	Serum levels to 8 hr	Unaffected	(106)
Erythromycin ethyl succinate	Coated tablets	SM	—	—	C	Serum levels to 12 hr and during multiple dosing	Increased	(108)
Erythromycin ethyl succinate	Suspension	SM	—	—	C	Serum levels to 12 hr and during multiple dosing	Increased	(108)

[a] Serum levels unchanged in patients with pernicious anemia in this study.

Studies in our laboratory (103) indicate that the absorption of erythromycin stearate not only is impaired by food but also is impaired after dosing with a small volume of water in fasted subjects. Following a single 500-mg dose, consisting of 2×250-mg coated tablets, mean peak plasma levels were 1.4 ± 1.3, 1.4 ± 0.8, and $1.2 \pm 0.8\ \mu g\ ml^{-1}$ when doses were administered immediately following high-carbohydrate, -fat, and -protein meals. The mean peak level in fasted subjects receiving the drug with 250 ml water was $3.0 \pm 0.9\ \mu g\ ml^{-1}$, but this value was reduced to $1.7 \pm 0.5\ \mu g\ ml^{-1}$ when the water volume was reduced to 25 ml. The areas under plasma level curves from 0 to 12 hr and from zero to infinite time were significantly greater for the 250-ml fasted treatment than for all other treatments.

Steady-state peak blood levels of erythromycin, during repeated doses of 250 mg erythromycin stearate every 6 hr, were reduced from $0.34 \pm 0.36\ \mu g\ ml^{-1}$ in 12 fasted subjects to $0.25 \pm 0.13\ \mu g\ ml^{-1}$ in nonfasted individuals (104). However, these differences were not significant ($P > 0.1$). In the same study, mean steady-state peak blood levels of antibiotic from equivalent repeated doses of erythromycin estolate were similarly, but again not significantly, reduced from $3.5 \pm 1.3\ \mu g\ ml^{-1}$ to $2.6 \pm 1.1\ \mu g\ ml^{-1}$ because of food.

Three single-dose studies, using suspension dosage forms, obtained similar circulating antibiotic levels in fasted and nonfasted subjects from oral doses of erythromycin stearate (105), erythromycin estolate (106,107), and erythromycin ethyl carbonate (106). The minimal effect of food on suspension dosage forms is probably due to easier mechanical dispersion and hence faster dissolution of suspended particles compared to tablets or capsules, and the relative ease with which the suspension passes from the stomach into the small intestine in the absence or presence of food.

The only example of food increasing the bioavailability of an erythromycin product is provided by erythromycin ethyl succinate (108). In a single-dose study in 24 subjects, 800 mg of erythromycin ethyl succinate was administered as a suspension 1 hr before or shortly after a standard meal. The mean peak serum level of antibiotic from the postprandial dose, $3.2 \pm 1.0\ \mu g\ ml^{-1}$, was significantly higher than that from the fasting dose, $2.2 \pm 0.9\ \mu g\ ml^{-1}$. Giving the drug after a meal also significantly increased the area under the 0–8 hr serum level curve from $5.0 \pm 2.5\ \mu g\ hr\ ml^{-1}$ to $10.7 \pm 3.4\ \mu g\ hr\ ml^{-1}$. Similar food-related increases in bioavailability were observed in 21 subjects when erythromycin ethyl succinate was administered as both single and repeated doses of film-coated tablets.

Thus the various erythromycin products react with food in different ways and to varying degrees. One of the major problems associated with erythromycin bioavailability studies, particularly with doses of the inactive erythromycin esters, is correct interpretation of blood level data.

Erythromycin estolate hydrolyzes slowly in the body and circulates partly as the ester and partly as the free base (109). The ester has different plasma protein and tissue binding characteristics than the base, and the two drug forms have different distribution volumes. To obtain meaningful ester and free base bioavailability comparisons, circulating levels of the two drug forms must be measured separately. Although this has not been done hitherto, the recent description of a method for separating and assaying erythromycin estolate and erythromycin base from biological fluids containing both compounds should provide a simple solution to this problem (110).

ALCOHOL

Previous studies on factors influencing alcohol absorption have recently been criticized by Lin *et al.* (111). These authors compared alcohol absorption in male subjects after single doses of 45 ml of 95% alcohol as the following treatments: A, fasting; B, after a light breakfast; C, after a heavy breakfast; D, after a steak meal; E, 1 hr after a heavy breakfast; F, 1 hr before a heavy breakfast. Sufficient blood samples were taken to describe complete blood alcohol profiles following all doses, and blood profiles were analyzed using Michaelis–Menten type elimination kinetics (112).

First-order absorption kinetics were observed from treatments A and F, and the respective absorption rate constant values were 3.1 hr^{-1} and 9.1 hr^{-1}. However, from all other treatments, alcohol absorption could not be described by simple kinetics. Peak blood alcohol levels were significantly reduced ($P < 0.05$) following treatments B, D, and E, compared to treatment A; times of peak levels were significantly increased following treatments B, C, and E; and total areas under blood level curves were significantly reduced following treatments B, C. D, and E. Because of the Michaelis–Menten type elimination kinetics, areas under blood level curves are influenced by the relationship

$$\frac{\text{instantaneous rate of alcohol metabolism}}{\text{amount of alcohol in the body}} = -\frac{V_m}{K_m + C} \tag{5}$$

where C is the blood alcohol concentration and K_m and V_m are Michaelis constants. The extents of reduction in areas from all treatments using the area from treatment A as the standard, and also the contribution of the relationship in equation 5 to area reduction, are reproduced in Table VI.

From their data, the authors conclude that both the rate and extent of alcohol absorption are inhibited by food, with reduction in the extent of

Table VI. Magnitude of Relative Effects Contributing to the Reduction in Mean Areas Under Blood Alcohol Concentration–Time Curves[a]

Treatment	Overall reduction in area	Absorption efficiency component[b]	Component due to absorption rate and MM kinetics[c]
A	0	0	0
B	0.36	0.18	0.18
C	0.63	0.34	0.29
D	0.55	0.31	0.24
E	0.56	0.31	0.25
F	0.18	0.12	0.06

[a]Reproduced with permission from *Res. Commun. Chem. Pathol. Pharmacol.* **13**:713–722 (1976).
[b]This component is calculated from relative asymptotic absorption plot ratios A_∞ / V_d, where A_∞ is the total amount of alcohol absorbed and V_d is the apparent distribution volume.
[c]This component is calculated from the difference between column 2 and column 3.

absorption contributing somewhat more than the rate. The greatest reductions in overall absorption efficiency were observed when alcohol was ingested immediately after a heavy breakfast or a steak meal and when it was taken 1 hr after a heavy breakfast. Inhibition was less following a light meal and was only slight when alcohol was ingested 1 hr before a meal.

A similar study was carried out in the reviewer's laboratory (113). However, in this study a smaller dose of 0.2 ml of 95% alcohol per kilogram of body weight was used. Alcohol was administered to six subjects in the fasted state and immediately following high-carbohydrate, -fat, or -protein meals.

Serum levels obtained from these treatments are summarized in Fig. 14. Food had a greater effect on alcohol absorption at the low dose used in this study. Areas under serum level curves from 0 to 3 hr were 1090 ± 257, 249 ± 162, 105 ± 109, and 47 ± 37 mg % hr from fasting, protein, fat, and carbohydrate treatments, representing mean reductions in overall absorption efficiency of 77%, 90%, and 96% due to the protein, fat, and carbohydrate meals, respectively. Marked reduction in alcohol absorption by carbohydrate has not been reported before.

The extent of inhibition of alcohol absorption by meals is therefore both dietary-component and dose dependent. Although the dose used in this study is relatively small, it is still an extremely large dose compared to those used in other drug–food interaction studies. The average equivalent dose of pure alcohol used per subject was 13 g. On a molar basis, this is equivalent to 50.7 g of aspirin and 125.2 g of tetracycline!

The serum level curves from postprandial doses of alcohol (Fig. 14) were too irregular for pharmacokinetic analysis. However, the fasted levels

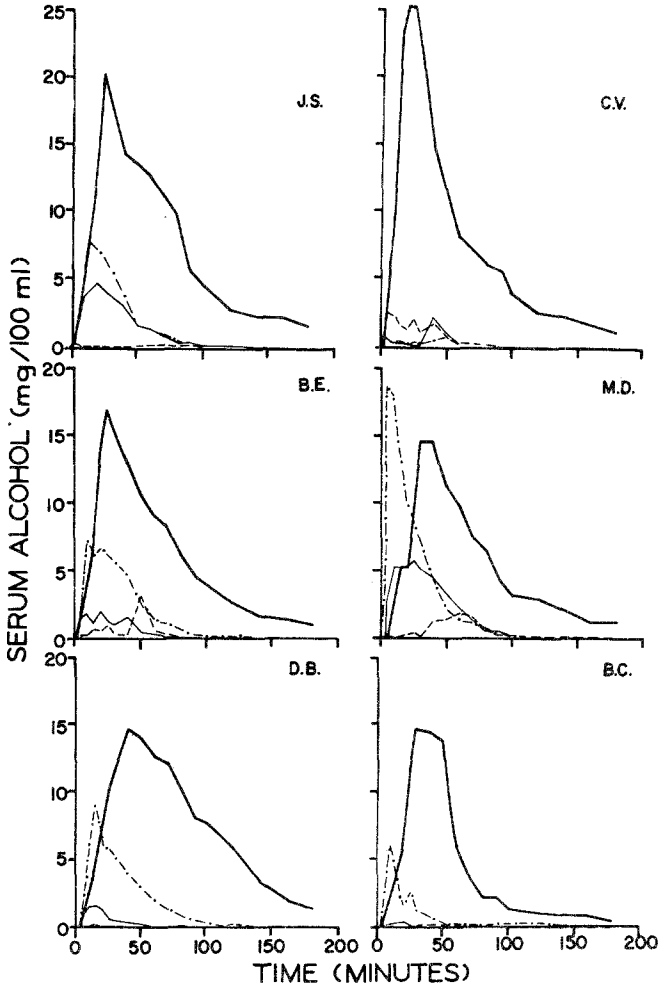

Fig. 14. Individual serum levels of alcohol following a dose of 0.2 ml of 95% alcohol per kilogram to fasted subjects (——) and following high-carbohydrate (- - - -), high-fat (——), and high-protein (–·–·–·) meals. Reproduced by permission from *J. Clin. Pharmacol.* **17**:199–206 (1977).

could be analyzed, and, because of the low dose of alcohol administered, elimination kinetics were described by a pseudo-first-order rate constant k_{el}, equivalent to the Michaelis function V_m/K_m (111,112). Best computer fits of data from all subjects were obtained using

$$C = \frac{k_0}{Vk_{el}}[1 - e^{-k_{el}(t-t_0)}]e^{-k_{el}t'} \tag{6}$$

where C is the alcohol concentration in serum, k_0 is a zero-order absorption rate constant, V is the apparent alcohol distribution volume, t is the total time from dosing during the absorption phase, t' is the time elapsed since absorption has stopped, and t_0 is the absorption lag time.

The concept of zero-order alcohol absorption is not new. Cooke (114) made a similar observation while studying alcohol absorption from the stomach in man. It is highly probable that, with the relatively small dose of alcohol used in our study, essentially all the dosed alcohol was absorbed directly from the stomach, resulting in zero-order kinetics.

Alcohol absorption in the absence and presence of food is obviously complex. Alcohol is efficiently absorbed from both the stomach and the intestine; it delays stomach emptying at high doses (115) and must undergo considerable but saturable first-pass metabolism during absorption. The considerable reduction in alcohol absorption due to food, particularly after low alcohol doses, may be due to slower absorption preventing saturation of hepatic enzymes, resulting in increased hepatic clearance during the first pass through the liver.

CONCLUSIONS

In this report, the reviewer has attempted to summarize the present knowledge regarding the influence of food and dietary components on drug absorption. No attempt has been made to look at "the other side of the coin" and to consider the influence of drugs on the absorption of food. Although these phenomena are closely related, the latter subject was outside the scope of this review but has been considered in some detail elsewhere (116).

During the preparation of this review, some major observations and questions have become apparent. The first observation is that food may have varied influences on drug absorption, from a significant increase—as with griseofulvin, nitrofurantoin, and lithium ion—to a marked decrease—as with ampicillin, propantheline, and some tetracyclines. It is also apparent—as observed with penicillin V and alcohol—that the time interval between eating and dosing can change the intensity of drug–food interactions. The reports on acetaminophen, alcohol, and propoxyphene also show that specific dietary components may influence drug absorption in different ways.

Two major questions one might ask are the following: is the present information for specific drugs of general application, i.e., are the reported data reliable? and are the observed changes in drug absorption of clinical significance?

Before answering the first question, it is important to recall that some cited studies were anecdotal in nature and the authors do not suggest that their observations are of general application. However, many studies gave

rise to specific recommendations regarding drug-food interactions and appropriate dosage regimens.

Evidence has been presented that drug–food interactions may vary with the type and size of meal, the time interval between eating and dosing, the volume of fluid ingested with a drug, and the physical and chemical forms in which the drug is dosed. However, in some studies these factors appear not to have been controlled, and their separate influences on drug absorption cannot be calculated. The significance of these studies is therefore uncertain.

The clinical significance of each drug–food interaction must be considered in the light of the degree of interaction and the pharmacological activity of the drug. In many cases, particularly with some antibacterial agents which normally circulate at concentrations well above the MIC values for susceptible organisms, observed interactions are probably not important. However, for drugs like some tetracyclines, propantheline, levodopa, and some penicillin and erythromycin products, drug–food interactions could cause depressed circulating drug levels and may result in therapeutic failure. Similarly, administration of griseofulvin, nitrofurantoin, and lithium with food is likely to increase their effectiveness in terms of increased circulating drug levels or reduced gastrointestinal irritation.

There is a need for more information on the influence of food, dietary components, and fluid volumes on drug bioavailability. Only when sufficient data are accumulated can patterns and mechanisms of physicochemical or physiological interactions be established that will enable dosage regimens to be optimized to ultimately benefit the patient.

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