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THE EFFECT OF FOOD ON DRUG BIOAVAILABILITY

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Roger D. Toothaker and Peter G. Welling

Center for Health Sciences, School of Pharmacy, University of Wisconsin, Madison, Wisconsin 53706

INTRODUCTION

The efficiency with which orally dosed drugs are absorbed into the systemic circulation and the influence of dosage form design have been of concern to clinical scientists, drug manufacturers, and regulatory agencies for a considerable time. The effects of food and fluid volume on the rate and extent to which oral dosage forms are absorbed, on the other hand, have until recently received scant attention.

Reviews on this subject (1, 2) have commented on drug-food interactions which may inhibit absorption to a degree where therapeutic effect is lost or may increase absorption to the point of toxicity. As most reported drug bioavailability studies in humans are carried out in fasting individuals, and indeed are required to be so by most regulatory agencies, the applicability of these data to the situation where a patient may ingest drugs and food in a more random fashion is questionable.

Food may influence drug absorption as a result of physiological changes in the GI tract or physical or chemical interactions between particular food components and drug molecules. Depending on the type and degree of interaction, drug absorption may be reduced, delayed, not affected, or increased by concomitant food intake.

Whether the changes in drug absorption are clinically significant depends both on the type of drug and the extent of the change. Clearly, a small alteration in absorption characteristics would be unimportant for a drug which is effective over a wide concentration range, but may be critical for a drug with a narrow therapeutic index or with a steep dose-response curve.

This review discusses the effects of food and fluid volume on drug bioavailability with particular reference to reports which have appeared since the original review (1), and also the clinical significance of observed changes.

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PHYSIOLOGICAL EFFECTS OF FOOD

The various mechanisms of drug absorption from the GI tract, methods of studying absorption, and physiological factors influencing drug bioavailability have recently been reviewed (3) and are not discussed here. Instead, attention is focused on physiological changes caused by food and fluid ingestion that may influence drug absorption.

Splanchnic Blood Flow

High protein liquid meals have been shown to increase the rate of estimated splanchnic blood flow (ESBF) while high glucose liquid meals cause a small and transient decrease (4). Passive drug absorption may be affected by an altered ESBF due to an increase or decrease in the transluminal concentration gradient. Drugs whose absorption is limited by luminal membrane transfer processes, however, should not be affected by changes in the ESBF.

Altered ESBF may also influence the absorption of drugs which are extensively metabolized due to changes in drug clearance during the first-pass through the hepatoportal system. This topic has recently been discussed by McLean et al (5). The systemic availability, F, of an abosrbed drug which is cleared solely by hepatic metabolism may be expressed as:

$$F = 1 - \frac{Q_{CL}}{Q}$$

where Q_{CL} is the hepatic clearance of drug and Q is the hepatic blood or plasma flow rate. For a constant clearance, an increase in the hepatic flow rate will increase the fraction of absorbed dose which is available to the circulation. However, if the increased hepatic flow rate is prolonged beyond the drug absorption time, the total area under the blood-level versus time curve may be unchanged due to the compensating effect of faster overall hepatic elimnation (6). There are also large individual differences in hepatic drug extraction efficiency and also in the sensitivity of the drug extraction ratio (Q_{CL}/Q) to changes in hepatic blood flow rates. Drugs with low extraction ratios might be expected to be relatively insensitive to altered hepatic blood flow, while the value of F may also be flow independent for drugs with very high extraction ratios.

Gastric Motility

Factors influencing gastric emptying have been reviewed by Bates & Gibaldi (7). While most gastric emptying studies have utilized liquid or semiliquid meals, their relevance to the situation with solid meals is uncertain. The studies of Hopkins (8) and Hunt (9) show that the presence of liquid food may increase the rate of stomach emptying, probably as a result of the

activation of tension receptors in the stomach wall. However, the predominant effect of food ingestion is that of inhibition of stomach emptying due to feedback mechanisms from the osmoreceptors, acid receptors, and fat and fatty acid receptors situated in the proximal small intestine (10).

Stomach emptying is delayed by hot meals (11), by solutions of high viscosity (12), and also by high fat, and, to a lesser extent, protein and carbohydrate meals (13). Solid meals in rats have been shown to almost double the stomach emptying time compared to liquid meals (14).

Thus ingestion of food may inhibit gastric emptying by one or more mechanisms, and may influence drug absorption to a variable extent. Prolonged residence in the acidic environment of the stomach is likely to delay dissolution of acidic compounds, and to accelerate dissolution of basic molecules. Although some acidic and neutral compounds are absorbed directly from the stomach, the optimal site for absorption is in the small intestine, and delayed stomach emptying is likely to cause a delay in drug absorption. Increased residence time in the stomach may also cause a reduction in the overall absorption efficiency for drugs which are either acid labile or are sensitive to the action of gastric enzymes.

On the other hand, compounds absorbed at specific intestinal sites, or by saturable active transport mechanisms, may exhibit increased absorption with delayed stomach emptying due to a decrease in the rate of which drug passes the active absorption site. Food reaching the small intestine stimulates intestinal motility and this may increase drug dissolution and also decrease the diffusional path of drug molecules to the intestinal epithelium. However, increased gastric motility may also lower absorption efficiency as a result of the increased transit rate of drug through the intestine.

Gastric Secretion

Ingestion of food increases the gastric secretion of hydrochloric acid and also of many enzymes that may affect drug dissolution and degradation. Sufficient hydrogen ion may be secreted during digestion to render the blood and urine alkaline. This phenomenon is referred to as the postprandial alkaline tide (15), and may affect the passage of ionizable compounds across the luminal membrane. Increased secretion of bile after food intake may accelerate the dissolution of poorly soluble compounds (16). However, drug absorption may be impeded by increased bile flow due to bile salt-drug complexation (7).

DRUG-FOOD INTERACTIONS

In addition to changes in drug absorption resulting from physiological effects, altered absorption may result also from direct drug-food or drug-fluid interactions.

Fluid Volume

Because the predominant driving force for the passive absorption of drugs is the drug concentration gradient across the epithelial and capillary membrane, it would appear axiomatic that drugs should be absorbed more efficiently from concentrated solutions than from dilute solutions. However, in the intact animal or human, the reverse appears to be the case. In animals, the toxicity of a large number of organic acids and bases, and also inorganic ions, increased with increasing compound dilution (17). The absorption of both sodium pentobarbital and salicylate has also been shown to be superior from dilute solutions compared to concentrated solutions (18). Increased absorption of drugs when administered with large fluid volumes compared to small fluid volumes in humans has also been demonstrated (1).

Several mechanisms have been proposed to explain increased drug absorption from dilute solutions. A concentrated drug solution may be sufficiently hypertonic to delay stomach emptying, while a larger fluid volume present in diluted drug solutions may stimulate stomach emptying due to the activation of gastric tension receptors, thus presenting the drug to the intestinal epithelial surface at a faster rate (18). A decreased solution osmolarity has also been shown to cause increased absorption of both ionized and un-ionized molecules from rat intestinal segments as a result of an increase in the net mucosal to serosal solvent flux (19).

Physical Interactions

Absorption or adsoprtion interactions between drug and food molecules may influence drug availability. Drug chelation by polyvalent metal ions frequently inhibits drug bioavailability (20), while other compounds have been shown to complex with proteins (21). Food may also act as a purely physical barrier, preventing drug access to the mucosal surface of the GI tract. This would, of course, affect both actively and passively absorbed compounds.

FORMULATION EFFECTS

As indicated in the original review (1), the formulation in which a drug is administered may have a profound effect on the extent of a particular drug-food interaction.

Suspensions and solutions are generally considered to be less susceptible to the action of food than other dosage forms because of their diffuse nature, greater mobility within the GI tract, and the relative ease with which they can diffuse from the stomach into the small intestine. With capsule and tablet dosage forms, not only is dissolution likely to be affected by the presence of food, but also the delay in gastric emptying due to the food is

likely to have a greater effect when the drug is contained in a single dosage unit. The possible physiological and physicochemical interactions due to the presence of food, as well as other influences on drug absorption, are summarized in Table 1.

CLASSES OF INTERACTIONS

Attention is focused here on reports appearing predominantly during the last two years. For detailed descriptions of drug-food interactions reported earlier, the reader is directed to two previous reviews (1, 2).

The reported effects of food on drug absorption are divided into those interactions which cause reduced, delayed, or increased absorption, and also those showing no effect due to the presence of food. As in the original review (1), the tables summarizing the drug-food interactions include details of drug dosage forms, fluid volumes, meals, the time sequence of eating and dosing, and also sampling procedures, where this information is available.

Drugs Whose Absorption May Be Reduced By Food

Recently reported interactions in this category are presented in Table 2. Food has previously been shown to decrease the overall bioavailability of a variety of antimicrobial agents (1, 2). More recent studies are consistent with this. Reduced absorption of this type of agent may be a particular problem in pediatric therapy because medication for this type of population often has to be accompanied by or mixed with food or milk in order to make it acceptable to the patient.

In a study comparing the absorption of oral antibiotics from suspensions when accompanied by milk or a children's formula, compared to the fasted state, McCracken et al (22) reported approximately 40% decreases in the 6 hr area under the blood-level versus time curve for cephalexin, penicillin G, and penicillin V. Reduced absorption of penicillin V and penicillin G from tablets and delayed absorption of cephalexin from capsules have been reported (1). Since suspensions should not give rise to significant dissolution problems, reduced absorption in this study is possibly due to acid catalyzed degradation of compounds in the stomach.

Watanakunakorn (23) provided further evidence of the erratic absorption characteristics of nafcillin after oral doses, but also demonstrated that circulating antibiotic levels were higher, more predictable, and were achieved at a faster rate in fasted individuals than when nafcillin was administered within 1 hr of a meal.

Extending previous studies on the inhibition of tetracycline absorption due to milk and milk products, Poiger (24) administered tetracycline cap-

Table 1 Physiological and physicochemical interactions due to ingested food and fluid which may influence drug absorption

Physiological interactions		
Physiological function	Effect of food on physiological function	Possible effect on drug absorption
Stomach emptying rate	Decreased rate with solid meals, fats, high temperature, acids, solutions of high osmolarity. Increased rate with large fluid volumes.	Absorption generally delayed, may be reduced with unstable compounds, may be increased due to drug dissolution in stomach. Absorption increased with large fluid volumes.
Intestinal motility	Increased	Faster dissolution and decreased diffusional path promotes absorption. Shorter transit time may inhibit absorption.
Splanchnic blood flow	Generally increased, but may be decreased by ingestion of glucose.	Absorption increased with faster blood flow. Variable effects on first pass metabolism, depending on drug characteristics.
Bile secretion	Increased	Absorption may increase due to faster dissolution or decreased due to complexation.
Acid secretion	Increased	Increased absorption of basic drugs provided they are acid stable. Decreased absorption of acid labile compounds.
Enzyme secretion	Increased	Increased or decreased absorption depending on drug characteristics.
Active absorption process	Increased	Active drug absorption reduced by competitive inhibition.

Physicochemical interactions	
Interaction	Possible effect on drug absorption
Fluid volume	Absorption rate may decrease with large fluid volumes due to reduced concentration gradient, but absorption efficiency may be increased due to faster dissolution, osmotic effect, and exposure of drug molecules to greater GI surface area.
Food and food components	Absorption decreased due to chelation, absorption, adsorption, physical blockade, but may be increased due to increased solubility with some diets. Variable effects due to pH changes.

Table 2 Drugs whose absorption may be reduced by food

Drug	Dosage form	Food	Water volume (ml)[a]	Time interval[b]	Sampling	Reference
Penicillin V	Suspension	Milk, children's formula	None	Immediately before	Serum to 6 hr	22
Penicillin G	Suspension	Milk, children's formula	None	Immediately before	Serum to 6 hr	22
Cephalexin	Suspension	Milk, children's formula	None	Immediately before	Serum to 6 hr	22
Nafcillin	Tablets	Breakfast?[c]	—[d]	Within 1 hr after	Serum to 6 hr	23
Tetracycline	Capsule	Milk	100	With meal	Urine to 30 hr	24
Erythromycin stearate	Film coated tablets	Carbohydrate, fat, and protein meals	20/250	Immediately after	Serum to 12 hr	25
Erythromycin[e] stearate	Film coated tablets	Standard breakfast	25/250	Immediately after	Plasma to 12 hr after during repeated dosing	26
ASA	Tablets	Carbohydrate, fat, and protein meals	25/250	Immediately after	Plasma ASA to 6 hr, SA to 12 hr	28
ASA	Enteric coated tablets	Standard breakfast	100	Immediately after	Plasma SA to 10 hr, urine to 48 hr	29
Phenacetin	Suspension	Green vegetables	—[d]	Before	Plasma to 7 hr	30
Antipyrine	Syrup	Green vegetables	—[d]	Before	Plasma to 30 hr	30
Antipyrine	—[d]	Charcoal beef	—[d]	Control diet[f]	Plasma[d]	31
Theophylline	—[d]	Charcoal beef	—[d]	Control diet	Plasma	31
Sotalol	Tablets	Breakfast, milk	50/50	With meal	Plasma to 32 hr, urine to 72 hr	32

[a] Volume of water ingested with the drug.
[b] Time of dosing in relation to the meal.
[c] Details of meal not given.
[d] Details not given.
[e] Single and repeated dose study.
[f] Relationship between times of eating and dosing not given.

sules to healthy volunteers in the presence of milk and also in the presence of milk and ethylene diamine tetraacetic acid (EDTA). As shown in Figure 1, cumulative urinary excretion of tetracycline was reduced by the presence of milk, while no reduction occurred when tetracycline was given either with EDTA alone or with combined milk and EDTA. Previous reported incidence of diarrhea associated with EDTA administration were avoided in this study by neutralizing EDTA solutions with sodium hydroxide or by combining EDTA disodium and tetrasodium salts.

Earlier reports that the absorption of erythromycin stearate from coated tablets is reduced by food have been confirmed in both single dose (25) and repeated dose (26) studies in healthy volunteers. In the single dose study, two tablets of erythromycin stearate were administered together with 250 ml of water to healthy individuals immediately following a high carbohydrate, fat, or protein meal, or with 20 or 250 ml of water to fasted individuals. The results of this study are summarized in Figure 2.

Although the absorption rate of erythromycin was not markedly affected by the various treatments, overall absorption efficiency of the antibiotic was markedly reduced following the nonfasting treatments, and by the small fluid volume, compared to the fasted dose given with the large fluid volume. Drug absorption was reduced 53–54% by food, and was reduced 43% by the small fluid volume. There was no significant difference in the relative effect of the various test meals on erythromycin absorption.

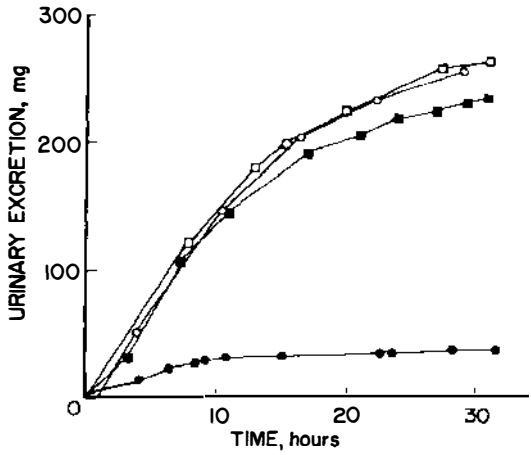

Figure 1 Cumulative amount of tetracycline excreted in urine of one individual after receiving a 500 mg capsule alone (○), with 500 mg EDTA (□), with 200 ml milk (●), or with 200 ml milk and 2.3 g EDTA (■). (Reproduced by permission from *Eur. J. Clin. Pharmacol.* 14:129–31, 1978.)

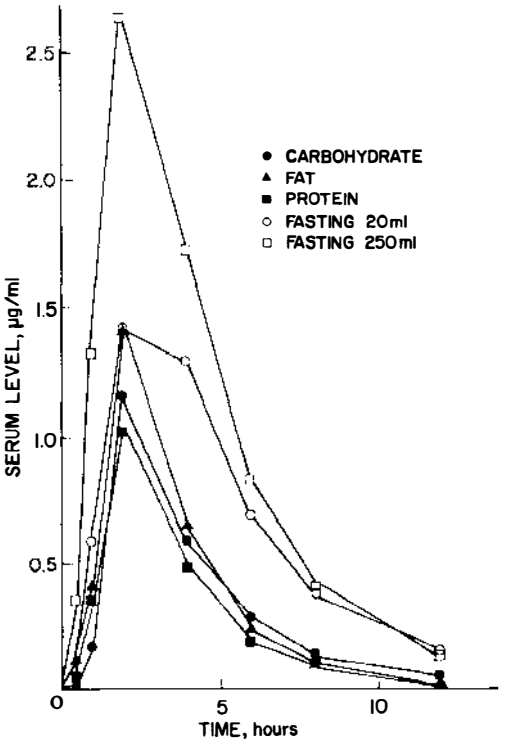

Figure 2 Mean serum levels of erythromycin in 6 subjects following single 500 mg doses of erythromycin stearate in tablets under fasting and nonfasting conditions. (Reproduced by permission from *J. Pharm. Sci.* 67:764–66, 1978.)

In a subsequent study, using a larger group of healthy volunteers and a different commercial brand of erythromycin stearate (26), erythromycin absorption was again shown to be reduced by the presence of food, and when accompanied by a small fluid volume in fasted subjects. This trend was also observed, although somewhat attenuated, following repeated doses. The results of the single and repeated dose studies are summarized in Figure 3. Contrary to the majority of evidence, Malmborg (27) reported that dosing erythromycin stearate in the presence of food results in faster absorption and increased peak antibiotic levels in the circulation, but no difference in the area under the erythromycin concentration in plasma curve, compared to values obtained in fasted subjects. This author suggests, despite considerable evidence to the contrary, that erythromycin stearate should be administered immediately following a meal in normal practice. No other literature was cited in that report; also, no details of either the type

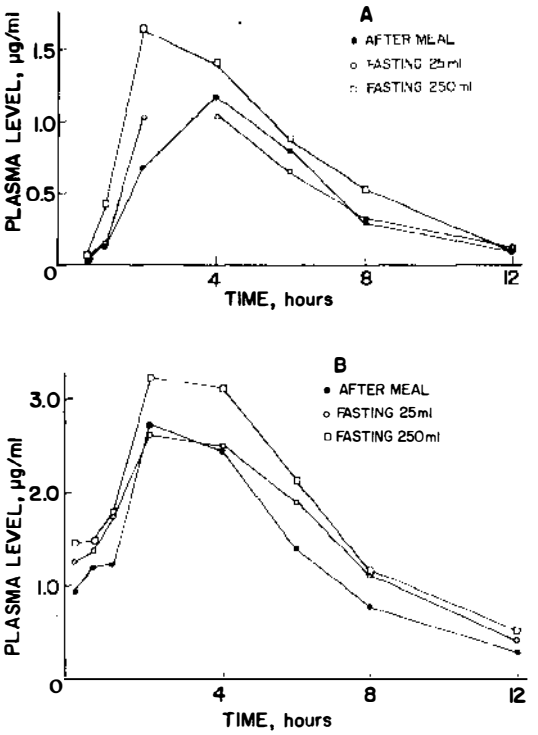

Figure 3 Mean plasma levels of erythromycin in 10 subjects following single (*A*) and repeated (*B*) 500 mg doses of erythromycin stearate in tablets under fasting and nonfasting conditions. (Reproduced by permission from *J. Pharm. Sci.* 68:150–55, 1979.)

of meal used, the volume of fluid ingested with the drug, or the source of erythromycin stearate were given.

Koch et al (28) studied the effect of food and fluid volumes on aspirin (ASA) absorption in healthy volunteers by measuring plasma levels of both ASA and salicylate (SA). Subjects received two tablets of ASA with 25 or 250 ml of water while fasting, or following standard carbohydrate, fat, or protein meals. ASA profiles in plasma following the various treatments are shown in Figure 4. Peak ASA levels were reduced 40–50% by food and the rate of absorption was also significantly reduced. Plasma ASA levels were decreased somewhat by the reduced water volume in fasted subjects, although not to the same extent as in the nonfasted treatments. While circulating levels of SA followed similar trends to those of ASA, differences in plasma profiles between treatments for this metabolite were not statistically significant. This is not unexpected, as ASA is chemically and metabolically unstable and rapidly hydrolyzes to SA both in the GI tract and during

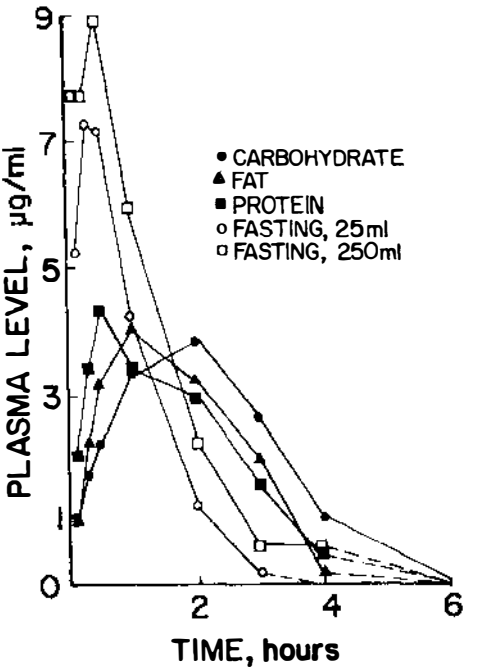

Figure 4 Mean plasma levels of ASA in 6 subjects following single 650 mg doses of ASA in tablets under fasting and nonfasting conditions. (Reproduced by permission from *J. Pharm. Sci.* 67:1533–35, 1978.)

absorption. SA, on the other hand, is chemically stable compared to ASA, and the absorption efficiency of this metabolite should be relatively insensitive to changes in stomach emptying time.

Enteric coated products are frequently associated with poor or erratic bioavailability. Bogentoft et al (29) compared the effect of food on the absorption efficiency of drug from enteric coated ASA tablets and also from a formulation of enteric coated ASA granules contained in capsules. Subjects received the dosage forms either while fasting or immediately following a standard breakfast. Plasma SA levels from the two formulations were similar under fasting conditions. Food appeared not to influence absorption from the granules (see Table 4), while the SA levels from the tablets were both decreased and delayed in nonfasted individuals (Figure 5). This study provides an example of the relatively minor effect that delayed stomach emptying due to food ingestion may exert on dispersed drug systems. However, as the analgesic effect of ASA resides predominantly in the unchanged form of the drug rather than in SA, bioavailability studies based solely on circulating levels or urinary excretion of the relatively inactive metabolite need to be interpreted with caution from a clinical viewpoint.

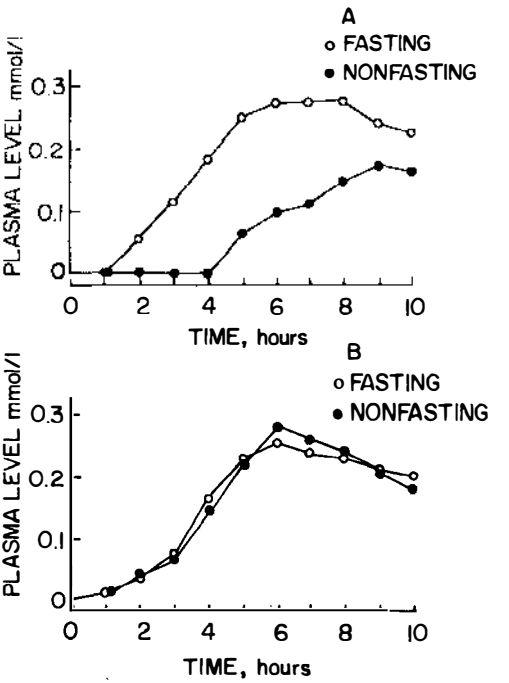

Figure 5 Mean plasma levels of SA in 8 subjects following single 1.0 g doses of ASA as enteric coated tablets (*A*) and enteric coated granules in capsules (*B*) under fasting and nonfasting conditions. (Reproduced by permission from *Eur. J. Clin. Pharmacol.* 14:351–55, 1978.)

Food may also cause a decrease in circulating drug levels by increasing metabolic activity. Pantuck et al (30) showed that some green vegetables, which are capable of increasing the activity of intestinal and hepatic metabolizing enzymes, can increase the metabolic clearance rate of antipyrine and phenacetin. Inclusion of the vegetables in the diet resulted in a 13% decrease in mean antipyrine plasma levels and an 11% increase in metabolic clearance, while the distribution volume was unaltered. All values returned to normal when a control diet was reinstated. The results for phenacetin showed considerable interindividual variation. However, mean phenacetin levels decreased by 34–67%, while areas under plasma curves were reduced by up to 87% when the vegetable diet was used. These values also returned toward normal with a control diet.

Kappas et al (31) reported similar metabolic effects with theophylline and antipyrine. Subjects were fed diets in which meat was either charcoal-broiled or cooked without exposure to charcoal, the latter representing control values. Metabolic clearance of theophylline was increased by 30%,

while that of antipyrine was increased by 38% during charcoal-broiled diets compared to controls. This was attributed to stimulation of hepatic metabolizing enzymes by the polycyclic hydrocarbons resulting from charcoal exposure.

The influence of various factors on the bioavailability of the β-adrenergic receptor antagonist, sotalol, was studied by Kahela et al (32). Test subjects received one 100 mg tablet of sotalol together with 50 or 500 ml of water while fasting, following a standard breakfast, and also with 500 ml of milk, 500 ml of calcium gluconate solution (30 mmol Ca^{2+}/liter), and 500 ml of ferrous sulfate solution (2.6 mmol Fe^{2+}/liter). Peak sotalol levels in plasma were significantly decreased by the standard meal and also by milk and calcium, although only the food and calcium treatments resulted in reduced areas under sotalol plasma profiles. The rate of sotalol absorption, represented by the time of maximum drug levels in plasma, was decreased following the calcium and also the large fluid volume treatments. The ferrous sulfate solution had little influence compared to the calcium gluconate solution on sotalol bioavailability. Although this suggests a specific interaction between the drug and calcium ion which does not occur with ferrous ion, the lack of effect by the ferrous sulfate solution may have been due to the low concentration of this salt. Why ingestion of sotalol with a large fluid volume should delay drug absorption is not clear. The authors' suggestion that the larger fluid volume caused a delay in gastric emptying, is inconsistent with the reports cited earlier (1) and also in this review (8–10), which have shown that gastric emptying is increased by large fluid volumes. It was concluded from this study that sotalol should be administered between meals and that calcium-containing additives should not be included in sotalol formulations.

Drugs Whose Absorption May Be Delayed By Food

Drug products which are reported to exhibit delayed absorption in the presence of food are listed in Table 3.

Cephalexin capsules were previously included in this category (1). More recently, Tetzlaff et al (33) examined the absorption characteristics of cephalexin from two different formulations in children suffering from osteomyelitis and septic arthritis. One group of children received capsules while fasting and also with a standard, but unspecified, meal. The other group similarly received the dose as a suspension. Plasma levels indicated very little effect by food on cephalexin absorption efficiency from either formulation. The rate of absorption from both treatments was faster from the suspension than from capsules, and the presence of food appeared to delay the absorption of drug from both dosage forms to a small extent. The observed delays in absorption were considered not to be clinically signifi-

Table 3 Drugs whose absorption may be delayed by food

Drug	Dosage form	Food	Water volume (ml)	Time interval	Sampling	Reference
Cephalexin[a]	Capsules	Standard hospital meal?	—	With meal	Serum to 5 hr	33
Cephalexin[a]	Suspension	Standard hospital meal?	—	With meal	Serum to 5 hr	33
Cefaclor	Capsule	Standard breakfast	—	After	Plasma and urine to 6 hr	34
Metronidazole	Tablets	Standard breakfast	100	Immediately after	Serum to 24 hr	35
ASA	Tablets	Standard breakfast	100	Immediately after	Plasma SA to 10 hr, urine to 48 hr	29
Alclofenac	Suspension	Standard breakfast	—	2 hr before, immediately before, 30 min after	Plasma to 10 hr, urine to 24 hr	37
Indoprofen	Capsules	Standard breakfast	—	Immediately after	Plasma to 8 hr, urine to 24 hr	38
Digoxin	Tablets	Standard breakfast	—	Immediately after, 90 min after	Plasma to 79 hr, urine to 10 days	39
Cimetidine	—	Standard breakfast	—	Immediately after	Blood to 24 hr	40

[a] Repeated dose study.

cant. A similar result was obtained in normal volunteers receiving cefaclor capsules (34). Subjects ingested the capsules with water, as desired, in the fasting state, and also following a standard breakfast. Although food caused a decrease in plasma levels of antibiotic, 6 hr cumulative urinary excretion was similar in the two treatments, indicating delayed rather than reduced absorption. The considerable intersubject variation of cefaclor absorption in this study may have been caused by the variable water intake permitted, and also by the relatively unstable nature of this compound.

The study on metronidazole absorption was conducted in healthy subjects and also in patients suffering from Crohn's disease (35). In the patients, metronidazole absorption was somewhat variable and reduced compared to that in normal volunteers. However, both groups showed plasma drug profiles which were slightly delayed but not reduced by the presence of food. Metronidazole appears to be another drug, like doxycycline and nitrofurantoin (1), which needs to be taken with food due to its irritant effect on the GI tract and whose absorption is fortuitously not inhibited to any clinical extent by food ingestion. Reduced absorption of other antimicrobial agents, cephalexin, lincomycin, erythromycin stearate, and rifampin, has also been reported in patients suffering from Crohn's disease (36).

Some anti-inflammatory drugs have exhibited delayed absorption in the presence of food. Alclofenac absorption was delayed in healthy subjects when administered immediately before or 30 min. after a standard breakfast (37). The absorption phase of plasma alclofenac profiles was also more accurately described by zero-order kinetics when the drug was administered with food, compared to first-order kinetics in the fasting state. A formulation effect was demonstrated in the interaction between food and indoprofen (38). In a study in healthy subjects, the absorption of indoprofen was significantly delayed when an encapsulated form of the drug was administered immediately following a standard meal. When the drug was administered as tablets, however, food tended to increase the rate of absorption somewhat, although the difference in this value between fasted and nonfasted treatments was not statistically significant, and had no effect on the extent of indoprofen absorption. It is suggested that the different effects observed with the two dosage forms may have been due to the rate limiting steps for absorption of capsules and tablets being respectively the rate of gastric emptying and the rate of tablet disintegration/dissolution.

A previous report that digoxin absorption from tablets was delayed by food (1) is confirmed in a more recent study by Johnson et al (39). These authors suggest that, because the therapeutic effect of digoxin may not be temporally related to drug levels in plasma due to relatively slow pentration into myocardial tissue and also because side effects such as nausea appear to correspond to the occurrence of peak plasma levels, administering

digoxin with food may result in decreased side effects without compromising therapeutic efficacy.

Whereas food was shown to have no effect on the absorption efficiency of cimetidine from tablets in patients with active peptic ulcers or severe gastritis, the rate of absorption was delayed to a small extent (40). An interesting observation in this study was that, while nonfasted patients exhibited a normal drug profile in blood, with the peak level occurring at about 2 hr, 8 out of 10 fasted patients exhibited bimodal drug profiles in blood with peaks occurring at 1 and 3–5 hr postdosing. The difference between the type of cimetidine blood profiles in fasted and nonfasted subjects is indicated in Figure 6. While several possible reasons for the bimodal blood cimetidine levels are advanced by the authors, the actual underlying mechanism is unresolved. Similar behavior to this has also been observed with acetaminophen (41).

Drugs Whose Absorption May Be Unaffected By Food

Recent reports showing a lack of effect of food on drug absorption are given in Table 4. A study in children confirmed previous observations (1) that absorption of erythromycin estolate from a suspension dosage form is unaffected by food (22). Absence of an effect of food was also observed with ampicillin suspension (22) and spiramycin (42).

No significant changes were observed in the absorption characteristics of propoxyphene, ASA, or phenazone from a combination tablet between fasting subjects and subjects receiving the tablet after a standardized breakfast (43). The refractory nature of propoxyphene absorption to food in this

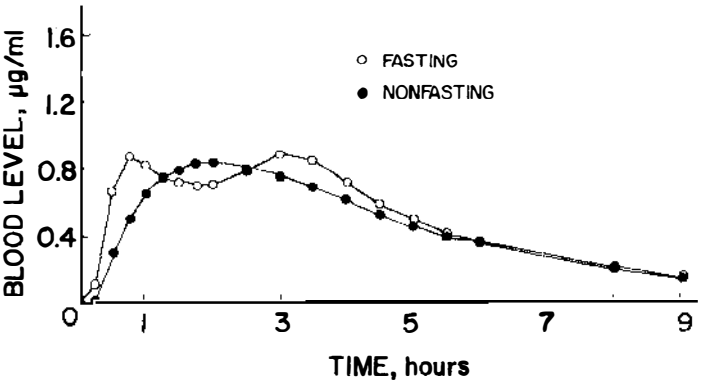

Figure 6 Mean blood levels of cimetidine in 10 patients following single 200 mg doses of cimetidine under fasting and nonfasting conditions. (Reproduced by permission from *Br. J. Clin. Pharmacol.* 7:23–31, 1979.)

Table 4 Drugs whose absorption may be unaffected by food

Drug	Dosage form	Food	Water volume (ml)	Time interval	Sampling	Reference
Ampicillin	Suspension	Milk, children's formula	None	Immediately before	Serum to 6 hr	22
Erythromycin estolate	Suspension	Milk, children's formula	None	Immediately before	Serum to 6 hr	22
Spiramycin	Tablets	Standard breakfast	100	With meal	Serum to 8 hr	42
Propoxyphene hydrochloride ASA Phenazone	Combination tablet	Standard breakfast	100	Immediately after	Plasma to 48 hr	43
ASA	Enteric coated granules in capsules	Standard breakfast	100	Immediately after	Plasma SA to 10 hr	29
Indoprofen	Tablets	Standard breakfast	▬	Immediately after	Plasma to 8 hr, urine to 24 hr	38
Propylthiouracil	Tablets	Standard breakfast	100	Immediately after	Serum to 5 hr	44
Oxazepam	Tablets	Standard breakfast	100	Immediately after	Serum to 48 hr	45
Bendroflu-methiazide	Tablets	Standard breakfast	150	With meal	Plasma to 24 hr, urine 48 hr	46

study is consistent with a previous report (1) that propoxyphene absorption was either unchanged or slightly increased as a result of the influence of standard meals. Comparison of the ASA absorption data to that obtained from ASA tablets alone (28) is not possible as circulating levels of ASA and SA were combined following the combination tablet.

Considerable intersubject variability obscured the detection of any possible effect of food on the absorption of propylthiouracil in healthy volunteers (44). Large differences were observed both in the rate and extent of drug absorption between fasting and nonfasting treatments and also within treatment groups. The authors conclude that as food effects are unpredictable, dosage individualization would increase the clinical efficacy of prophylthiouracil. Other studies by Melander et al (45) and Beerman et al (46) failed to show any effect of food on the absorption characteristics of oxazepam and bendroflumethiazide.

Drugs Whose Absorption May Be Increased By Food

Drug products in this category are listed in Table 5. Increased absorption of erythromycin ethylsuccinate from a suspension dosage form in children, when administered immediately before milk or a children's formula (22), is consistent with earlier reports that food increases the absorption of this drug form (1). In the pediatric study (22), serum concentrations of erythromycin in nonfasted individuals were 30–80% higher than in fasted individuals.

The absorption of erythromycin estolate, measured both as the unhydrolyzed ester and also as the free base, was shown to be increased by the presence of food in normal volunteers (26). The plasma profiles obtained are reproduced in Figure 7. Following the single dose, peak plasma levels, times of peak levels, and also area values are all significantly increased by the nonfasted treatment. This trend was maintained after repeated dosing, but the differences in peak levels and areas did not reach the 5% significance level. Since the estolate form of erythromycin is relatively acid stable compared to the free base, it is reasonable to suspect that delayed stomach emptying due to food may delay absorption, but may also increase the overall absorption efficiency due to a greater fraction of the dosed compound dissolving in the stomach before it passes into the small intestine.

Increased dissolution resulting from delayed stomach emptying has also been suggested to give rise to increased absorption of macrocrystalline and microcrystalline nitrofurantoin (1, 2). Increased absorption of this drug in nonfasted individuals has been confirmed by Mannisto (47) in a study using nitrofurantoin tablets of medium crystal size with low and high fat diets. Urinary excretion of unchanged nitrofurantoin was greatly increased by the high lipid meal, and to a lesser extent by the low lipid meal, but was

Table 5 Drugs whose absorption may be increased by food

Drug	Dosage form	Food	Water volume (ml)	Time interval	Sampling	Reference
Erythromycin ethylsuccinate	Suspension	Milk, children's formula	None	Immediately before	Serum to 6 hr	22
Erythromycin estolate[a]	Capsules	Standard breakfast	25/250	Immediately after	Plasma to 12 hr and during multiple dosing	26
Erythromycin stearate[a]	Film coated tablets	Breakfast?	—	Immediately before	Plasma to 7.5 hr	27
Nitrofurantoin	Tablets	Standard low lipid meal	200	With meal	Serum to 14 hr, urine to 20 hr	47
Diftalone	Capsules	"Standard Italian lunch"	Half glass	Immediately after	Plasma to 96 hr, urine to 96 hr	48
8-Methoxsalen	Coated tablets	Standard breakfast	100	After	Plasma to 6 hr	49
Propranolol	—	Standard breakfast	100	Immediately after	Serum to 8 hr	50
Metoprolol	—	Standard breakfast	100	Immediately after	Plasma to 8 hr	50
Dicoumarol	Tablets	Standard breakfast	50	With meal	Serum to 72 hr	51
Diazepam	Tablets	Standard breakfast	30	Immediately after	Plasma to 48 hr	52
Hydrochloro-thiazide	Tablets	Standard breakfast	150	With meal	Plasma to 24 hr, urine to 48 hr	53

[a] Single and repeated dose study.

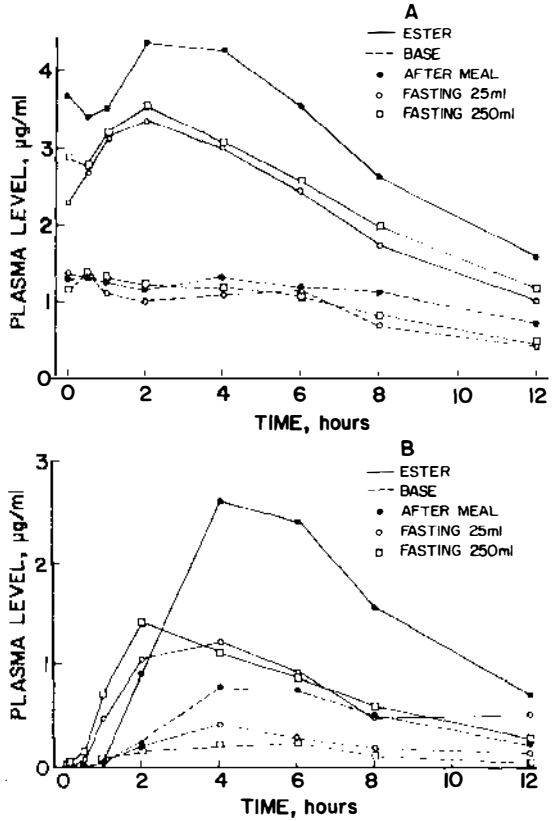

Figure 7 Mean plasma levels of erythromycin-2'-propanoate and erythromycin base in 10 subjects following repeated (*A*) and single (*B*) doses of erythromycin estolate capsules at a dose level equivalent to 500 mg erythromycin base under fasting and nonfasting conditions. (Reproduced by permission from *J. Pharm. Sci.* 68:150–55, 1979.)

decreased by the presence of antacids. Food also decreased peak circulating levels of nitrofurantoin, which provides another possible advantage of reduced systemic side effects with this compound in addition to the lower incidence of local gastric irritation in the presence of food.

Another possible example of delayed stomach emptying causing increased drug availability is suggested in a study by Tenconi et al (48). These authors examined the absorption of diftalone from capsules in fasted subjects and also in subjects following a "standard Italian lunch." Administering the drug directly after the meal resulted in a 2.6-fold increase in peak circulating drug levels and a 2.8-fold increase in overall bioavailability compared to fasting conditions. The results were similar whether the meal and drug were both administered at 8 A.M. or at noon. Diftalone has

extremely low water solubility, and dissolution should be enhanced by delayed stomach emptying or by increased bile flow following ingestion of food.

The absorption efficiency of 8-methoxsalen, a compound used in combination with ultraviolet radiation for the treatment of psoriasis, was increased when the drug was taken after a standard breakfast compared to the fasted condition (49). As 8-methoxsalen is completely metabolized in the body, it was proposed that increased absorption may be related to decreased hepatic clearance. The dosage of 8-methoxsalen has to be adjusted in relation to the intensity of ultraviolet radiation in clinical practice, so it is important that the drug is dosed under similar conditions during both the initial dose-radiation calibration and during the subsequent treatment. It is suggested therefore that this compound should be administered in identical fashion during both the range finding and treatment dosages.

The absorption of two drugs with capricious absorption characteristics, propranolol and metoprolol, was increased in subjects who received the drugs following a standard breakfast (50). The mean circulating profiles are reproduced in Figure 8. While the absorption of both compounds was variable, values tended to be more consistent when the drugs were ingested

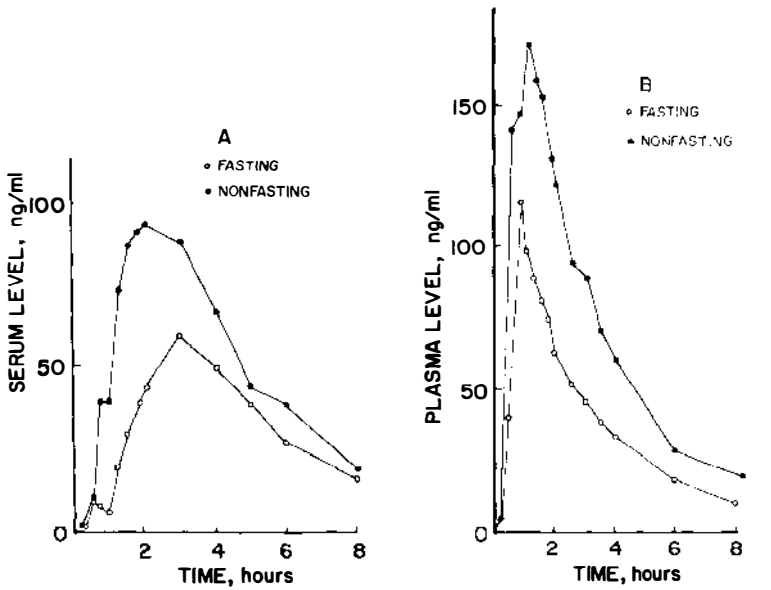

Figure 8 Concentrations of (*A*) propranolol in serum and (*B*) metoprolol in plasma in two subjects following single doses of 80 mg propranolol or 100 mg metoprolol under fasting and nonfasting conditions. (Reproduced by permission from *Clin. Pharmacol. Ther.* 22:108–12, 1977.)

in the nonfasting state. Although the increased absorption of these compounds was thought to be related in some way to changes in hepatic blood flow or in first-pass metabolism by the liver, no attempts were made to further elucidate the mechanisms involved.

Increased absorption of both dicoumarol (51) and diazepam (52) has been attributed to either increased dissolution, caused by delayed stomach emptying, or to greater solubilization of drug due to increased bile flow for dicoumerol, or increased gastric acid secretion for diazepam. Increased absorption of hydrochlorothiazide in the presence of food, on the other hand, could not be attributed to enhanced dissolution as the solid dosage form of this drug gave rise to similar bioavailability characteristics as did a solution in fasted individuals (53). Any metabolic effect is also excluded with this drug as it is eliminated largely unchanged by the kidneys. An alternative explanation which was proposed is that enhanced absorption may be related to the slower presentation of drug to the absorption sites of the small intestine after postprandial doses. Whatever the mechanisms involved, the increase in hydrochlorothiazide absorption in the presence of food is unlikely to be clinically significant owing to the relatively flat dose-reponse curve for this drug.

CLINICAL SIGNIFICANCE OF DRUG BIOAVAILABILITY CHANGES IN THE PRESENCE OF FOOD

The degree of change in clinical response due to altered drug bioavailability, whatever the cause, will be a function of the mode of drug action and also the extent of change in the rate and extent of drug absorption. It may be difficult to identify altered clinical effects owing to the likelihood of more than one drug being taken by a patient, with the associated possibility of drug interactions, and also the many other variables contributing to, and the subjective nature of assessing, clinical response.

Drugs for which uniformity of dosing is important, and which are likely to exhibit variable clinical response associated with bioavailability changes, are those with narrow therapeutic indices or steep dose-response relationships, drugs which have well-defined blood or tissue levels for therapeutic activity, compounds with serious dose-related side effects or which are absorbed by saturable site-specific processes. Drugs with short biological half-lives are also likely to be affected to a considerable extent by food because delayed absorption can give rise to a marked reduction in circulating blood levels.

While specific cases of detrimental changes in therapeutic effect due to altered drug bioavailability in the presence of food have not been docu-

mented, the potential exists for such changes for all compounds meeting the above criteria. The problem is of course one of degree. While it may be reasonably assumed that the therapeutic effect of drugs that do not meet the above criteria is unlikely to be influenced by bioavailability changes, it is clear that some clinical change will occur with all drugs and dosage forms provided the change in bioavailability is sufficiently large.

In the original review it was suggested, considering both the mechanism and degree of drug-food interactions and also the nature of the compounds involved, that clinical effects might well be expected with drugs such as tetracycline, levodopa, and some penicillin and erythromycin products, where drug-food interactions might cause sufficient depression in circulating drug levels to cause therapeutic failure (1). Conversely, administration of drugs such as griseofulvin and nitrofurantoin with food is likely to increase their clinical effectiveness due to higher circulating or urinary drug levels. From another viewpoint, the clinical effectiveness of nitrofurantoin, doxycycline, and lithium is clearly increased when considered in terms of reduced GI irritation and local side effects when these drugs are administered with food. Digoxin, whose absorption from tablets is delayed but not reduced by food, may also fit into this last category.

A considerable number of the interactions considered in the present review are therefore likely to have clinical consequences. The penicillins and cephalosporins are generally cleared relatively quickly from the circulation, and blood levels of these agents may be considerably reduced by food even when absorption is only delayed rather than reduced. The absorption of ASA is delayed by food, and circulating levels of this drug are considerably reduced. On the other hand, circulating levels of the antipyretic metabolite SA are only slightly influenced by food.

Because of the need to titrate the dosages of 8-methoxsalen and concomitant ultraviolet radiation for the treatment of psoriasis, any change in absorption of this agent is likely to be deleterious with regard to its clinical efficacy. The influence of food on drug metabolism (30, 31) represents an interesting new concept in the consideration of drug-food interactions. Clearly with the possible short- and long-range effects of induced or inhibited enzyme systems, and also changes in regional blood flow, food not only may influence the absorption of drugs but also may affect their distribution and elimination characteristics.

CONCLUSIONS

The material considered in this review has provided further evidence of the variable and often unpredictable manner in which direct and indirect drug-food interactions may influence drug absorption. As in the original review

of this subject (1) the ingestion of food before or at the same time as drug administration has been shown to decrease, delay, or increase drug absorption, or to have no effect. The importance of drug formulation in determining the type and extent of drug-food interaction is again suggested, as indicated with ASA and cephalexin. However, an earlier suggestion (1) that suspension dosage forms may generally be less sensitive to the effects of food is not entirely supported by the present literature, as suspension dosage forms appear in Tables 2, 3, 4, and 5.

While the mechanistic basis for reduced or delayed drug absorption in the presence of food can be readily understood in terms of such phenomena as delayed stomach emptying, physical and chemical interactions between drug molecules and food components, and drug degradation by GI secretion, the rationale put forward to explain increased drug absorption is less well defined. While increased splanchnic blood flow, and also less efficient hepatic extraction during the first-pass may be important mechanisms for some compounds, they are unlikely to influence the absorption of drugs which are metabolized to only a small extent. Certainly two of the most important factors that may lead to an increase in drug absorption from postprandial dosages are increased drug dissolution in the stomach during delayed gastric emptying and the greater motility of the small intestine.

Apart from the reduced local toxicity resulting from administration of drugs such as nitrofurantoin, lithium, and doxycycline with food, and the increased absorption of griseofulvin in the presence of fatty meals, there is little information on clinical changes related to drug-food interactions. However, from the frequency with which food is shown to cause marked changes in circulating levels and urinary excretion of many classes of drugs and the magnitude of some of the observed effects, it is clear that interactions between drug dosage forms and food, whether direct or indirect, are of potential clinical significance. The problem of such interaction needs further investigation in terms of the changes that occur and the conditions causing them, the underlying mechanisms involved, the importance of such interactions in the official regulation of drug use and, of paramount importance, their significance in relation to the administration of drug dosage forms to provide predictable and reliable therapy in clinical practice.

SUMMARY

The recent literature concerning interactions between ingested food and orally administered drugs, and the resulting effects on the rate and extent of drug absorption, has been reviewed. As was observed previously (1, 2) food has been shown to have a variable effect on drug absorption, and the observed changes are not entirely predictable from a mechanistic viewpoint.

While drug-food interactions are shown to give rise to a variety of effects, the majority of reported interactions give rise to either reduced or delayed drug profiles in the circulation.

With some drugs such as nitrofurantoin, doxycycline, and lithium, the presence of food increases clinical efficacy by reducing the incidence of local GI side effects. While there appear to be no reports of increases or decreases in the actual therapeutic efficacy of drugs due to food, the frequency of food related changes in drug bioavailability, and the magnitude of some of the effects, suggests that observed changes in drug absorption are likely to have profound clinical consequences particularly with drugs that have low therapeutic indices, steep dose-response curves, or clearly defined therapeutic or toxic levels in the body.

The review provides further evidence of the need for greater control in the relationship between drug administration and food ingestion.

Literature Cited

1. Welling, P. G. 1977. Influence of food and diet on gastrointestinal drug absorption: A review. *J. Pharmacokinet. Biopharm.* 5:291–334
2. Melander, A. 1978. Influence of food on the bioavailability of drugs. *Clin. Pharmacokinet.* 3:337–51
3. Forth, W., Rummel, W. 1975. *International Encyclopedia of Pharmacology and Therapeutics, Pharmacology of Intestinal Absorption: Gastrointestinal Absorption of Drugs.* Sect. 39B, Vol. 1. New York: Pergamon, 446 pp.
4. Brandt, J. L., Castleman, L., Ruskin, H. D., Greenwald, J., Kelly, J. J., Jones, A. 1955. The effect of oral protein and glucose feeding on splanchnic blood flow and oxygen utilization in normal and cirrhotic subjects. *J. Clin. Invest.* 34:1017–25
5. McLean, A. J., McNamara, P. J., duSouich, P., Gibaldi, M., Lalka, D. 1978. Food, splanchnic blood flow, and bioavailability of drugs subject to first-pass metabolism. *Clin. Pharmacol. Ther.* 24:5–10
6. Perrier, D., Gibaldi, M. 1974. Clearance and biologic half-life as indices of intrinsic hepatic metabolism. *J. Pharmacol. Exp. Ther.* 191:17–24
7. Bates, T. R., Gibaldi, M. 1970. *Current Concepts in the Pharmaceutical Sciences: Biopharmaceutics,* ed. J. Swarbrick, pp. 57–99. Philadelphia: Lea & Febiger. 304 pp.
8. Hopkins, A. 1966. The pattern of gastric emptying: A new review of old results. *J. Physiol. London* 182:144–49
9. Hunt, J. N., MacDonald, I. 1954. The influence of volume on gastric emptying. *J. Physiol. London* 126:459–74
10. Hunt, J. N., Knox, M. T. 1968. *Handbook of Physiology, Alimentary Canal,* ed. C. F. Code, 4:1917–35. Washington DC: Am. Physiol. Soc. 2343 pp.
11. Davenport, H. W. 1961. *Physiology of the Digestive Tract,* pp. 166. Chicago: Chicago Year Book. 230 pp.
12. Levy, G., Jusko, W. 1965. Effect of viscosity on drug absorption. *J. Pharm. Sci.* 54:219–25
13. Bachrach, W. H. 1959. Physiology and pathologic physiology of the stomach. *Ciba Found. Symp.* 11:3–28
14. Marcus, C. S., Lengemann, F. W. 1962. Absorption of ^{45}Ca and ^{85}Sr from solid and liquid food at various levels of the alimentary tract of the rat. *J. Nutr.* 77:155–60
15. Ganong, W. F. 1977. *Review of Medical Physiology,* pp. 363. Los Altos: Lange. 599 pp. 8th ed.
16. Gibaldi, M., Feldman, S. 1970. Mechanisms of surfactant effects on drug absorption. *J. Pharm. Sci.* 59:579–89
17. Ferguson, H. C. 1962. Dilution of dose and oral toxicity. *Toxicol. Appl. Pharmacol.* 19:164–68
18. Borowitz, J. L., Moore, P. F., Yim, G. K. W., Miya, T. S. 1971. Mechanism of enhanced drug effects produced by dilution of the oral dose. *Toxicol. Appl. Pharmacol.* 19:164–68
19. Ochsenfahrt, H., Winne, D. 1974. The contribution of solvent drag to the intestinal absorption of the acidic drugs

benzoic acid and salicylic acid from the jejunum of the rat. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 281:197–217

20. Dearborn, E. H., Litchfield, J. T., Jr., Eisner, H. J., Corbett, J. J., Dunnett, C. W. 1957. The effects of various substances on the absorption of tetracycline in rats. *Antibiot. Med.* 4:627–41
21. Kohn, K. W. 1961. Mediation of divalent metal ions in the binding of tetracycline to macromolecules. *Nature* 191:1156–58
22. McCracken, G. H. Jr., Ginsburg, C. M., Clahsen, J. C., Thomas, M. L. 1978. Pharmacologic evaluation of orally administered antibiotics in infants and children: Effect of feeding on bioavailability. *Pediatrics* 62:738–43
23. Watanakunakorn, C. 1977. Absorption of orally administered nafcillin in normal healthy volunteers. *Antimicrob. Agents Chemother.* 11:1007–9
24. Poiger, H., Schlatter, C. 1978. Compensation of dietary induced reduction of tetracycline absorption by simultaneous administration of EDTA. *Eur. J. Clin. Pharmacol* 14:129–31
25. Welling, P. G., Huang, H., Hewitt, P. F., Lyons, L. L. 1978. Bioavailability of erythromycin stearate: Influence of food and fluid volume. *J. Pharm. Sci.* 67:764–66
26. Welling, P. G., Elliott, R. L., Pitterle, M. E., Corrick-West, H. P., Lyons, L. L. 1979. Plasma levels following single and repeated doses of erythromycin estolate and erythromycin stearate. *J. Pharm. Sci.* 68:150–55
27. Malmborg, A. 1978. Absorption of erythromycin stearate after oral administration. *Curr. Med. Res. Opin.* 5:Suppl. 2, pp. 15–18
28. Koch, P. A., Schultz, C. A., Wills, R. J. Hallquist, S. L., Welling, P. G. 1978. Influence of food and fluid ingestion on aspirin bioavailability. *J. Pharm. Sci.* 67:1533–35
29. Bogentoft, C., Carlsson, I., Ekenved, G., Magnusson, A. 1978. Influence of food on the absorption of acetylsalicylic acid from enteric coated dosage forms. *Eur. J. Clin. Pharmacol.* 14:351–55
30. Pantuck, E. J., Pantuck, C. B., Garland, W. A., Min, B. H., Wattenberg, L. W., Anderson, K. E., Kappas, A., Conney, A. H. 1979. Stimulatory effect of brussel sprouts and cabbage on human drug metabolism. *Clin. Pharmacol. Ther.* 25:88–94
31. Kappas, A., Alvares, A. P., Anderson, K. E., Pantuck, E. J., Pantuck, C. B., Chang, R., Conney, A. H. 1978. Effect of charcoal-broiled beef on antipyrine and theophylline metabolism. *Clin. Pharmacol. Ther.* 23:445–50
32. Kahela, P., Anttila, M., Tikkanen, R., Sundquist, H. 1979. Effect of food, food constituents and fluid volume on the bioavailability of sotalol. *Acta Pharmacol. Toxicol.* 44:7–12
33. Tetzlaff, T. R., McCracken, G. H. Jr., Thomas, M. L. 1978. Bioavailability of cephalexin in children: Relationship to drug formulations and meals. *J. Pediatr.* 92:292–94
34. Glynne, A., Goulbourn, R. A., Ryden, R. 1978. A human pharmacology study of cefaclor. *J. Antimicrob. Chemother.* 4:343–48
35. Melander, A., Kahlmeter, G., Kamme, C., Ursing, B. 1977. Bioavailability of metronidazole in fasting and non-fasting healthy subjects and in patients with crohn's disease. *Eur. J. Clin. Pharmacol.* 12:69–72
36. Parsons, R. L., Paddock, G., Hossack, G., Hailey, D. M. 1976. Pharmacology of antibiotics, *9th* Int. Congr. Chemother., London, 1975. *Chemotherapy,* ed. J. D. Williams. A. M. Geddes, 4:229. New York: Plenum. 436 pp.
37. Sennello, L. T., Sonders, R. C., Friedman, N. 1978. Effect of food on kinetics of the nonsteroidal antiinflammative, alclofenac. *Clin. Pharmacol. Ther.* 23: 414–20
38. Tamassia, V., Corvi, G., Moro, E., Tosolini, G. P., Fuccella, L. M. 1977. Effect of food on absorption of indoprofen administered orally to man in two dosage forms. *Int. J. Clin. Pharmacol.* 15:389–93
39. Johnson, B. F., O'Grady, J., Sabey, G. A., Bye, C. 1978. Effect of a standard breakfast on digoxin absorption in normal subjects. *Clin. Pharmacol. Ther.* 23:315–19
40. Bodemar, G., Norlander, B., Fransson, L., Walan, A. 1979. The absorption of cimetidine before and during maintenance treatment with cimetidine and the influence of a meal on the absorption of cimetidine—studies in patients with peptic ulcer disease. *Br. J. Clin. Pharmacol.* 7:23–31
41. Clements, J. A., Heading, R. C., Nimmo, W. S., Prescott, L. F. 1978. Kinetics of acetaminophen absorption and gastric emptying in man. *Clin. Pharmacol. Ther.* 24:420–31
42. Kamme, C., Kahlmeter, G., Melander, A. 1978. Evaluation of spiramycin as a

therapeutic agent for elimination of nasopharyngeal pathogens. *Scand. J. Infect. Dis.* 10:135–42
43. Melander, A., Berlin-Wahlen, A., Bodin, N. O., Danielson, K., Gustafsson, B., Lindgren, S., Westerlund, D. 1977. Bioavailability of D-proproxyphene, acetyl salicylic acid, and phenazone in a combination tablet (Doleron®): Interinvididual variation and influence of food intake. *Acta Med. Scand.* 202:119–24
44. Melander, A., Wahlin, E., Danielson, K., Hanson, A. 1977. Bioavailability of propylthiouracil: Interindividual variation and influence of food intake. *Acta Med. Scand.* 201:41–44
45. Melander, A., Danielson, K., Vessman, J., Wahlin, E. 1977. Bioavailability of oxazepam: Absence of influence of food intake. *Acta Pharmacol. Toxicol.* 40:584–88
46. Beerman, B., Groschinsky-Grind, M., Lindstrom, B. 1978. Effect of food on the bioavailability of bendroflumethiazide. *Acta Med. Scand.* 204:291–93
47. Mannisto, P. 1978. The effect of crystal size, gastric content and emptying rate on the absorption of nitrofurantoin in healthy human volunteers. *Int. J. Clin. Pharmacol.* 16:223–28
48. Tenconi, L. T., Buniva, G., Beretta, E., Pagani, V. 1977. Influence of food intake on the [redacted] of diftalone in man. *Int. J. [redacted] Pharmacol.* 15: 485–91
49. Ehrsson, H., Nilsson, S. O., Ehrnebo, M., Wallin, I., Wennersten, G. 1979. Effect of food on kinetics of 8-methoxsalen. *Clin. Pharmacol. Ther.* 25:167–71
50. Melander, A., Danielson, K., Schersten, B., Wahlin, E. 1977. Enhancement of the bioavailability of propranolol and metoprolol by food. *Clin. Pharmacol. Ther.* 22:108–12
51. Melander, A., Wahlin, E. 1978. Enhancement of dicoumerol bioavailability by concomitant food intake. *Eur. J. Clin. Pharmacol.* 14:441–44
52. Greenblatt, D. J., Allen, M. D., Mac Laughlin, D. S., Harmatz, J. S., Shader, R. I. 1978. [redacted] absorption: Effect of antacids [redacted] *Clin. Pharmacol. Ther.* 24:600–9
53. Beerman, B., Groschinsky-Grind, M. 1978. Gastrointestinal absorption of hydrochlorthiazide enhanced by concomitant intake of food. *Eur. J. Clin. Pharmacol.* 13:125–28