3

Gastrointestinal Absorption—Biologic Considerations

Drugs are most commonly given orally and the gastrointestinal tract plays a major role in determining the rate and extent of drug absorption. In this chapter, the more important biologic factors that influence drug absorption are considered.

MEMBRANE PHYSIOLOGY

The gastrointestinal barrier that separates the lumen of the stomach and intestines from the systemic circulation and the sites of drug action is a complex structure composed of lipids, proteins, lipoproteins, and polysaccharides. The barrier has the characteristics of a semipermeable membrane, permitting the rapid passage of some chemicals while retarding or preventing the passage of others. Amino acids, sugars, fatty acids, and other nutrients required for life readily cross the barrier in the healthy individual. At the same time the barrier can be highly restrictive. For example, there is virtually no leakage of plasma protein into the gastrointestinal tract in the healthy mammalian adult. Certain toxins, which would produce lethal effects if present in the circulation in minute quantities, are harmless if ingested because of their inability to traverse the barrier. Most drugs used in clinical practice are administered orally and must cross this barrier before reaching the systemic circulation. Thus, the characteristics of the gastrointestinal barrier are of considerable importance in biopharmaceutics.

Lipid-soluble molecules as well as small, hydrophilic molecules and ions are readily absorbed from the gastrointestinal tract in an apparently passive manner. Certain larger polar molecules with molecular weights up to several hundred are also absorbed but in a manner suggesting the active participation of components of the membrane. Accordingly, the biologic membrane may be viewed as a dynamic lipoid sieve, a semipermeable lipoid membrane containing numerous aqueous pores or channels, too small to be seen, and a host of carrier molecules that shuttle back and forth across the membranes like ferries.

Lipid-soluble molecules penetrate the barrier directly through the fat-like portion of the lipoprotein membrane. The aqueous pores render the epithelial membranes freely permeable to water, to monovalent ions, and to hydrophilic solutes of small molecular size such as urea. By introducing aqueous solutions of molecules of graduated size into the human intestine, and by determining the facility of absorption, it has been estimated that the hypothetical pores in the proximal intestine (jejunum) have an average radius of 7.5 A (7.5×10^{-7} mm) and those in the distal intestine (ileum), one of about 3.5 A.[1] The molecular size of most drug molecules suggests that pore transport is of minor importance in drug absorption.

The digestive end products of dietary carbohydrates and proteins are hexose and amino acid molecules that are water soluble but usually too large to flow easily through the system of pores. The carriers in the membrane transport these water-soluble substances through the lipid, perhaps by interacting with the solute to render it temporarily fat soluble.

Membrane transport of drugs and other chemicals directly through the lipid or aqueous channels is called *passive diffusion*. Carrier-mediated transfer of polar molecules is called *facilitated diffusion* or, in some cases, *active transport*.

Passive Diffusion

The transfer of most drugs across biologic membranes occurs by passive diffusion from a region of higher concentration to one of lower concentration. Passive transport is described by Fick's first law which states that the rate of diffusion across a membrane (dC/dt) is proportional to the difference in drug concentration on each side of the membrane (ΔC); that is,

$$-dC/dt = k\,\Delta C = k(C_1 - C_2) \quad (3\text{–}1)$$

where C_1 and C_2 denote the drug concentrations on each side of the membrane and k is a proportionality constant. By convention, we assume that $C_1 > C_2$ and that there is net transport of drug from region 1 to region 2. The proportionality constant incorporates the diffusion coefficient of the drug, the thickness and area of the biologic membrane, and the permeability of the membrane to the specific drug.

The gastrointestinal absorption of a drug from an aqueous solution requires diffusion in the lumen to the gut wall and penetration of the epithelial barriers to the capillaries of the systemic circulation. Upon emerging in the blood, the drug distributes rapidly into an apparent volume that is usually considerably larger than blood volume. Thus, during absorption, drug concentration in the blood will be much lower than at the absorption site. In essence, the general circulation functions like a sink for the drug in the gastrointestinal tract, and a large concentration gradient is maintained throughout the absorption phase; that is, $C_1 >> C_2$. Consequently, the concentration gradient (ΔC) is nearly equal to C_1, and Equation 3–1 may be rewritten as

$$-dC/dt \cong k\,C_1 \quad (3\text{–}2)$$

which is the familiar form of a first-order rate equation.

The gastrointestinal absorption of most drugs from solution may be described by first-order kinetics; the rate of absorption is proportional to drug concentration over a wide concentration range indicating passive absorption. For example, the absorption rate of hydrocortisone from the human small intestine is proportional to the concentration of the drug over a 2000-fold concentration range (from 0.05 to 100 mg/L).[2] The passive absorption process is driven solely by the effective concentration gradient that exists across the gastrointestinal barrier.

Carrier-Mediated Transport

Although most drugs are absorbed from the gastrointestinal tract by passive diffusion, certain compounds of therapeutic interest and many substances of nutritional concern are absorbed by an apparently *carrier-mediated* transport mechanism.

Active absorption takes place when the intestine transports a substance *uphill* against a concentration gradient. This phenomenon is easily demonstrated by placing identical solutions of glucose on either side of an excised segment of intestine. After a while, if the segment is kept viable, the concentration of glucose is found to be decreased on the mucosal (lumen) side, whereas its concentration on the serosal side has increased over the initial level. The epithelial cells have apparently pumped glucose uphill. *Facilitated diffusion* takes place when the intestine transports certain solutes *downhill* but at rates much greater than would be anticipated based on the polarity of the solute and its molecular size.

Active or facilitated absorption is usually explained by assuming that carriers in the lipoprotein membranes of the intestinal epithelial cells are responsible for shuttling these solutes in a mucosal-to-serosal direction. The major substances that are believed to be actively transported are sodium, other ions such as calcium and iron, glucose, galactose, amino acids, bile salts, and vitamin B_{12}. A larger number of substances, including other vitamins, such as riboflavin and thiamine, and certain drugs, are believed to be absorbed by facilitated diffusion.

The number of apparent carriers in the intestinal membranes is limited. Therefore, the rate of carrier-mediated transport must be described by the following equation:

$$\text{Absorption rate} = \frac{V_{max}C}{K_M + C} \quad (3\text{–}3)$$

where C is the solute concentration at the absorption site and V_{max} and K_M are constants. At low solute concentrations, such that $K_M >> C$,

$$\text{Absorption rate} = \frac{V_{max}}{K_M}C = k\,C \quad (3\text{–}4)$$

and apparent first-order kinetics are observed. Under these conditions there are a sufficient number of carriers so that a constant proportion of solute molecules presented to the epithelial surface is transported. As the solute concentration increases

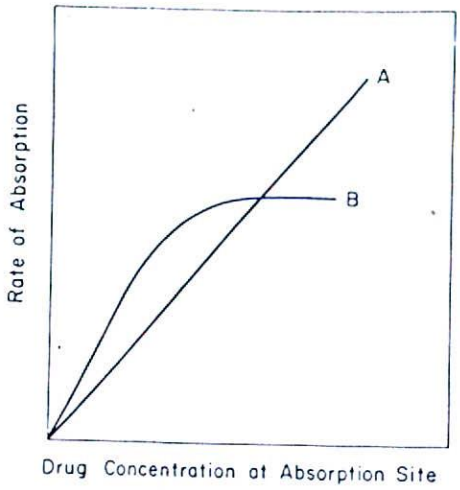

Fig. 3–1. Relationship between absorption rate and drug concentration for a passive process (curve A) and a carrier-mediated process (curve B).

the number of unoccupied carriers is reduced and the proportion of solute molecules that actually gets across the membrane declines until a maximum absolute number is reached. When $C >> K_M$, then

$$\text{Absorption rate} = V_{max} \qquad (3\text{–}5)$$

Further increases in solute concentration are not associated with any increase in the rate of absorption.

Absorption rate-concentration relationships for carrier-mediated and passive diffusion processes are shown in Figure 3–1. The plot describing the passive process is linear over the entire concentration range (see Eq. 3–2). The absorption rate of a substance that is transported by active absorption or facilitated diffusion shows linear dependence on concentration only at low concentrations (see Eq. 3–4). As the concentration increases the rate of ascent of the curve decreases, and eventually the absorption rate becomes invariant with concentration (see Eq. 3–5). The plateau region of the curve reflects saturation of the carrier mechanism. This type of rate process is termed a *capacity-limited process*.

There appear to be several carrier-mediated transport systems in the small intestine. Each is characterized by both structural and site specificity. For example, amino acids and monosaccharides such as glucose and galactose are absorbed in a specialized fashion but by different carrier systems. The amino acid system is specific and strongly favors the transport of the L-stereoisomeric form as opposed to the D-form of amino acids. The hexose system requires the particular molecular configuration of glucose; a wide variety of other 6-carbon sugars are unacceptable to the carrier. Independent carrier-mediated processes have been identified for the absorption of bile salts and pyrimidines.

Competition between two similar substances for the same transfer mechanism and inhibition of absorption of one or both compounds are other characteristics of carrier-mediated transport. Inhibition of absorption may also be observed with agents, such as sodium fluoride, cyanide, or dinitrophenol, that interfere with cell metabolism.

If the structure of a drug is sufficiently similar to that of a substance absorbed by carrier-mediated transport, there is the likelihood that the drug may also be absorbed in this manner. Methyldopa and levodopa are both absorbed by active transport via an amino acid transport mechanism. Penicillamine, an amino acid analog used in the treatment of Wilson's disease and lead poisoning, is actively transported across the rat intestine.[3] Uphill transport is found with the L-isomer but not with the D-form. Active transport of penicillamine is decreased in the presence of cyanide and certain L-amino acids. Serine and threonine derivatives of nitrogen mustard, which have been investigated for antitumor activity, are also absorbed by a carrier-mediated process.[4] Another antitumor agent, 5-fluorouracil, is actively transported across the small intestine by the pyrimidine transport system.[5]

Some substances may be absorbed by simultaneous carrier-mediated and passive transport processes. Certain pyrimidines such as uracil and thymine are a case in point.[6] The contribution of each process to the total absorption rate varies with concentration. The contribution of the carrier-mediated process to the overall absorption rate decreases with concentration and at sufficiently high concentrations is negligible.

The capacity-limited characteristics of carrier-mediated processes suggest that the bioavailability of a drug absorbed in this manner should decrease with increasing dose. Figure 3–2 shows that the relative availability of riboflavin in man decreases with increasing amounts of administered vitamin.[7] Above a certain dose, the *amount* of riboflavin absorbed remains constant regardless of the size of the dose. Similar findings are reported for thiamine

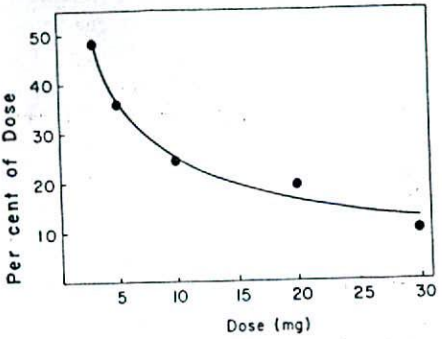

Fig. 3–2. Relative bioavailability of riboflavin (expressed as percent of dose) as a function of oral dose administered to fasting subjects. (Data from Levy, G., and Jusko, W.J.[7])

and ascorbic acid.[8,9] The use of large single oral doses of these vitamins is irrational. If relatively large daily doses are required, one should use divided doses.

GASTROINTESTINAL PHYSIOLOGY

The major components of the gastrointestinal tract are the stomach, small intestine, and large intestine or colon (Fig. 3–3). The small intestine includes the duodenum, jejunum, and ileum. The major segments of the gastrointestinal tract differ from one another both anatomically and morphologically, as well as with respect to secretions and pH.

The stomach is a pouch-like structure lined with a relatively smooth epithelial surface. Extensive absorption of weakly acidic or nonionized drugs and certain weakly basic drugs can be demonstrated in the stomach under experimental conditions. Ethanol is rapidly and completely absorbed from the ligated stomach pouch of the dog. Similar findings with sulfaethidole and barbital have been reported in surgically altered rats.[10] However, under normal conditions, when gastric emptying is not impeded, the stomach's role in drug absorption is modest. The absorption of aspirin and ethanol from the human stomach after oral administration of aqueous solutions to healthy subjects has been estimated to be about 10% and 30% of the dose, respectively.[11,12] In each case, the balance of the dose is absorbed from the small intestine.

The small intestine is the most important site for drug absorption in the gastrointestinal tract. The epithelial surface area through which absorption can take place in the small intestine is extraordinarily large because of the presence of villi and microvilli, finger-like projections arising from and forming folds in the intestinal mucosa. The irregularities in the mucosal surface caused by the microvilli, villi, and submucosal folds increase the area available for absorption by more than 30 times that which would be present if the small intestine were a smooth tube.[13] Based on studies in the rat, one can estimate that the effective surface area of the small intestine is about 10 times that of the stomach.[10] Other studies conclude that surface area decreases sharply from proximal to distal small intestine. The surface area in man has been estimated to range from 80 cm^2/cm serosal length just beyond the duodenojejunal flexure to about 20 cm^2/cm serosal length just before the ileocecal valve.[14] There is also a progressive decrease in the average

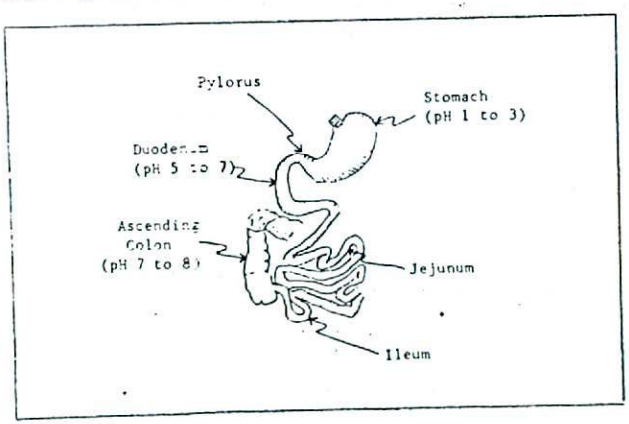

Fig. 3–3. Representation of the human gastrointestinal tract.

size of aqueous pores from proximal to distal small intestine and colon.[1,15]

The small intestine is also the most important region of the gastrointestinal tract with respect to carrier-mediated transport. The proximal small intestine is the major area for absorption of dietary constituents including monosaccharides, amino acids, vitamins, and minerals. However, both vitamin B_{12} and bile salts appear to have specific absorption sites in the ileum.[16]

The large intestine, like the stomach, has a considerably less irregular mucosa than that of the small intestine. This segment serves as a reserve area for the absorption of drugs that have escaped absorption proximally because of their physiochemical properties or their dosage form (e.g., enteric-coated tablets and sustained-release products). The large intestine is not an ideal absorption site, however, and incomplete absorption may result if a large fraction of the dose of a drug reaches the colon. On the other hand, the large intestine may play an important role in the efficacy of orally administered drugs, such as sulfasalazine, that require metabolism (reduction) by intestinal bacteria in the ileum and colon for bioactivation.

Gastrointestinal Blood Flow

The blood perfusing the gastrointestinal tract plays an important role in drug absorption by continuously maintaining the concentration gradient across the epithelial membrane. The dependence of intestinal absorption on blood flow rate changes from blood flow-independent to blood flow-limited as the absorbability of the substance increases.[17] Polar molecules that are slowly absorbed show no dependence on blood flow; the absorption of lipid soluble molecules and molecules that are small enough to easily penetrate the aqueous pores is rapid and highly dependent on the rate of blood flow. The absorption rate of most drugs probably shows an intermediate dependence on blood flow rate; relatively large decreases from normal mesenteric blood flow rate are required to produce an important change in absorption rate. In general, the rate of drug absorption is unaffected by normal variability in mesenteric blood flow. Ordinarily, changes in mesenteric blood flow that result from disease or drug effects must be substantial and sustained to significantly influence drug absorption.

The entire blood supply draining most of the gastrointestinal tract returns to the systemic circulation by way of the liver. Therefore, the entire dose of a drug that is given orally and completely absorbed is exposed to the liver before reaching the bloodstream. Since the liver is the most important organ in the body for drug metabolism and metabolizes some drugs rapidly, there is the possibility that a large fraction of the dose will never reach the systemic circulation because of hepatic metabolism during absorption. This phenomenon is known as the hepatic first-pass effect and is responsible for the less-than-complete bioavailability of many drugs given orally. Metabolism of a drug during absorption by enzymes found in the gut wall may also reduce bioavailability. A more detailed discussion of these aspects of drug metabolism is presented in Chapter 8.

Gastrointestinal pH

There may be as much as a 10 million-fold difference in hydrogen ion concentration between the stomach and the colon. An exceedingly abrupt, 10 thousand-fold difference in hydrogen ion concentration exists between the stomach and the duodenum. The pH at the absorption site is an important factor in drug absorption because many drugs are either weak organic acids or bases. In solution, organic electrolytes exist in a nonionized (usually lipid-soluble) and an ionized (usually poorly lipid-soluble) form. The fraction of each species depends on the pH of the solution. Since the gastrointestinal barrier (as well as many other barriers and membranes in the body) is much more permeable to uncharged, lipid-soluble solutes, a drug may be well absorbed from one segment of the gastrointestinal tract, where a favorable pH exists, but poorly absorbed from another segment, where a less favorable pH is found. The absorption of weakly basic drugs such as antihistamines and antidepressants is favored in the small intestine where such drugs exist largely in a nonionized form. On the other hand, the acidic gastric fluids tend to retard the absorption of weak bases but promote the absorption of weakly acidic drugs such as sulfonamides and nonsteroidal anti-inflammatories. Changes in the pH of the fluids in a given segment of tract may improve or impede the absorption of a drug.

The pH of gastric fluid varies considerably. Gastric secretions have a pH of less than 1, but the pH of gastric contents is usually between 1 and 3 because of dilution and diet. The pH of the stomach contents is distinctly but briefly elevated after a meal; pH values of 5 are not unusual. Fasting tends

to decrease the pH of gastric fluids. Disease may also influence the pH of the stomach. The average gastric pH is significantly lower in patients with a duodenal ulcer than in healthy individuals. Fats and fatty acids in the diet have been found to inhibit gastric secretions. A major clinical effect of antispasmodic drugs, such as atropine and propantheline, and H_2-blockers, such as cimetidine and ranitidine, is a reduction in gastric acid. Some anticholinergic activity, including suppression of gastric secretions, is commonly found with many other drugs. Antacid products are widely used for the purpose of neutralizing gastric acidity and elevating the pH of gastric contents. Disease or drug-related changes in gastric pH may influence the dissolution, stability, and/or absorption of certain drugs.

GASTRIC EMPTYING AND GASTROINTESTINAL MOTILITY

In theory, weakly acidic drugs should be better absorbed from the stomach than from the intestine, because a larger fraction of the dose is in a non-ionized, lipid-soluble form. However, the limited residence of the drug in the stomach and the relatively small surface area of the stomach more than balance the influence of pH in determining the optimal site of absorption. Thus, factors that promote gastric emptying tend to increase the absorption rate of all drugs. The converse is also true. Slow gastric emptying can delay the onset of effect of drugs such as analgesics or sedatives in situations requiring prompt clinical response. Prompt gastric emptying is important for drugs that are unstable in stomach fluids because of low pH or enzyme activity. For example, the extent of degradation of penicillin G after oral administration depends on its residence time in the stomach and on the pH of the stomach fluids.

Gastric emptying often appears to be an exponential process. Standard low bulk meals and liquids are transferred from the stomach to the duodenum in an apparent first-order fashion, with a half-life of 20 to 60 min in the healthy adult. However, many factors can influence the rate of this process. Gastric emptying is retarded by fats and fatty acids in the diet, high concentrations of electrolytes or hydrogen ion, high viscosity or bulk, mental depression, lying on the left side, diseases such as gastroenteritis, pyloric stenosis, gastric ulcer, gastroesophageal reflux, Crohn's disease, celiac disease, and hypothyroidism, and during the luteal phase of the menstrual cycle. Many drugs including atropine and propantheline, narcotic analgesics, amitriptyline, imipramine, desipramine, chlorpromazine, and aluminum hydroxide can also retard gastric emptying. Propantheline has been found to double the mean gastric half-emptying time of a test meal in man.[18] After placebo the mean half-emptying time was 68 min and after 30 mg of propantheline bromide it was 135 min. Gastric emptying is promoted by fasting or hunger, alkaline buffer solutions, anxiety, lying on the right side, diseases such as hyperthyroidism, and drugs such as metoclopramide, a dopaminergic blocker, widely used for nausea and vomiting associated with cancer chemotherapy.

Gastric emptying of liquids is much faster than that of food or solid dosage forms. It has been found in normal subjects that complete gastric emptying of enteric-coated barium granules, administered in a standard breakfast, requires about 4 to 8 hr.[19] When considering the emptying of a single object from the stomach, such as an enteric-coated tablet, terms such as half-life are meaningless. Emptying of a single unit is a random process. Intact tablets have been observed in the stomach as long as 6 hr after ingestion of an enteric-coated product with a meal.[20]

Gastric emptying is one of the more important factors contributing to the unusually large intersubject variability in the absorption of drugs from enteric-coated tablets. As a means of reducing this variability, it has been suggested that enteric-coated medication be administered in the form of small, individually coated granules that would empty gradually but continuously into the duodenum.[21]

Differences in gastric emptying among patients also contribute to the variability in absorption rate of drugs from conventional dosage forms. For example, after administration of 1.5 g (3 tablets) acetaminophen to 14 convalescent hospital patients, the maximum concentration in the plasma ranged from 7.4 to 37.0 μg/ml, and the time required to reach the maximum concentration ranged from 30 to 180 min.[22] Both these indices of absorption rate were linearly related to the gastric emptying half-life found in each patient (Fig. 3–4). Despite the marked variability in absorption rate, little difference in the extent of absorption of acetaminophen was found among patients. A similar correlation between absorption rate and gastric emptying has been observed in man with cimetidine.[23]

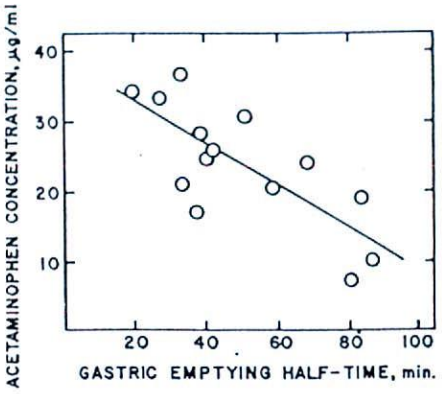

Fig. 3–4. Relationship between peak concentration of acetaminophen in plasma and gastric emptying half-time after a single oral dose. Rapid gastric emptying results in high peak levels. (Data from Heading, R.C., et al.[22])

Posture, which affects gastric emptying, also affects the absorption of acetaminophen.[24] Acetaminophen absorption was markedly delayed in all subjects lying on the left side compared to that observed when the same subjects were ambulatory (Fig. 3–5). This effect must be taken into account in drug absorption studies conducted in hospitalized patients.

Tablets and capsules are commonly swallowed with little or no water and many patients in bed swallow them lying down. Under these conditions, a solid dosage form may lodge in the esophagus and stay there until it disintegrates. This may cause damage to the esophageal mucosa, leading to ulceration and later to stricture or perforation.

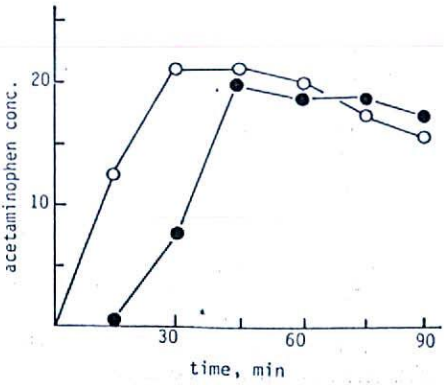

Fig. 3–5. Mean acetaminophen concentrations in plasma (µg/ml) after a single oral dose to ambulatory (○) and supine (●) subjects. The supine position results in delayed gastric emptying and absorption of acetaminophen. (Data from Nimmo, W.S., and Prescott, L.F.[24])

Esophageal ulceration has been described for many drugs including aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), slow-release KCl, tetracycline, doxycycline, clindamycin, quinidine, and iron salts. One case report[25] cites a patient with mild asthma who on one occasion, after forgetting to take the evening dose of slow-release theophylline, swallowed his medication without water when he went to bed. The tablets seemed to lodge in his esophagus; he ignored this sensation, swallowed several times, and went to sleep. On awakening, the patient experienced severe, sharp retrosternal pain; this persisted for 2 weeks. A large local esophageal erosion was identified on esophagoscopy and the patient was treated with hourly antacids; symptoms resolved within one week.

Slow esophageal transit also delays drug absorption. Twenty patients awaiting cardiac catheterization swallowed a single tablet containing acetaminophen and barium sulfate. The first 11 subjects swallowed the tablet with up to 15 ml water while supine; the tablet's progress down the esophagus was followed by fluoroscopy. In 10 of these subjects, transit of the tablet was delayed in the esophagus. The 9 subjects who followed, swallowed the tablet while standing; in all cases, it entered the stomach immediately.[26]

The mean peak plasma concentration of acetaminophen in the patients who experienced no esophageal delay was 8.8 µg/ml and the median time to peak was 35 min, whereas mean peak concentration was 5.9 µg/ml and median time to peak was 105 min in those where tablet transit was delayed in the esophagus. When there is delayed esophageal transit, absorption in the first 60 min is much less than when normal transit occurs.

Patients should be advised that tablets and capsules must be taken with several swallows (at least 2 ounces) of water or other beverages, while standing or sitting upright. This is particularly important for drugs that may damage the esophageal mucosa or that need to be absorbed rapidly to induce sleep or relieve pain.

On the basis of aspirin absorption studies, it has been suggested that migraine causes a significant delay in gastric emptying.[27] Thirty minutes after 900 mg of effervescent aspirin the mean plasma salicylate concentration in 35 patients during a mi-

graine attack was 5 mg/100 ml, compared with a value of about 7 mg/100 ml in 14 control patients. Impairment of absorption correlated with the severity of the headache and the gastrointestinal symptoms at the time of treatment. There is the possibility that severe pain in general may retard gastric emptying.

The effect of acute migraine attack on the absorption of tolfenamic acid, an NSAID, was studied in 7 female patients.[28] Migraine attacks delayed absorption. At 2 hr after oral administration mean drug concentration in plasma was about 4 μg/ml in the absence of an attack but only 1.8 μg/ml during an attack; mean peak concentrations were found at 2 hr and 4 hr, respectively. These findings are probably the result of the delay in gastric emptying that accompanies a migraine attack. Rectal metoclopramide accelerates gastric emptying and absorption of oral tolfenamic acid; the combination may be useful for the treatment of migraine in certain patients.

Not only is gastric emptying an important determinant of the overall absorption rate, in some cases it may be rate limiting. In other words, the apparent absorption rate constant of a drug determined from pharmacokinetic studies may actually equal the first-order rate constant for gastric emptying. This hypothesis was recently tested and confirmed by simultaneously measuring gastric emptying and the rate of appearance in blood of acetaminophen after oral administration to healthy subjects.[29] The emptying pattern and the plasma acetaminophen concentration-time profile were closely related. For example, when the start of gastric emptying was delayed, there was a corresponding lag period during which the plasma concentration did not rise or rose slightly. On the other hand, the most rapid increases in plasma acetaminophen concentrations were found when a substantial proportion of the dose emptied in an initial squirt. In those cases where gastric emptying could be described as a simple monoexponential process, there was agreement between the apparent absorption rate constant (determined from the blood data) and the gastric emptying rate constant (Fig. 3–6). These findings confirm that gastric emptying, rather than transmucosal transfer from the lumen of the small intestine, is the rate-limiting step in the absorption of acetaminophen given orally in solution. In all cases, the calculated rate constant for transfer of drug from the small intestine to the bloodstream was greater than the rate constant for gastric emptying. Once the drug reached the small intestine, absorption was rapid (mean absorption half-life of about 7 min).

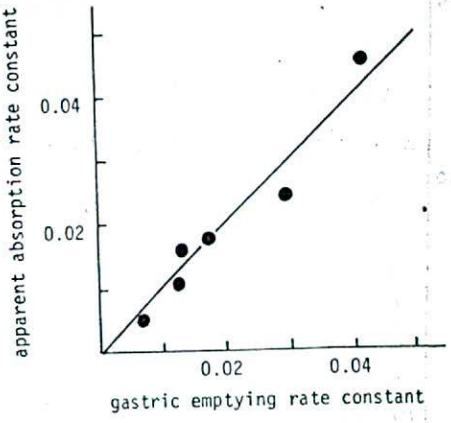

Fig. 3–6. Relationship between the apparent absorption rate constant (min^{-1}) and the gastric emptying rate constant (min^{-1}) after a single oral dose of acetaminophen in healthy subjects who emptied the drug from their stomachs in a monoexponential manner. The line of identity is shown. Under certain conditions, the absorption rate of a drug is rate-limited by gastric emptying. (Data from Clements, J.A., et al.[29])

There are many examples of the influence of drugs that affect gastric emptying on the absorption rate of other drugs administered concomitantly (Fig. 3–7). Propantheline has been found to reduce the absorption rate of riboflavin, sulfamethoxazole, ethanol, and acetaminophen.[30–33] Intramuscular administration of meperidine or heroin produces a profound delay in the gastric emptying and absorption of acetaminophen.[34] On the other hand, metoclopramide increases the absorption rate of ethanol,[32] acetaminophen,[33] tetracycline,[35] and pivampicillin.[36] In most of these cases, there is little effect on the extent or completeness of absorption.

The motility of the small intestine as indicated by small bowel transit time also plays a role in drug absorption. The mean transit time of unabsorbed food residues or insoluble granules through the human small intestine is estimated to be about 4 hr.[37]

Intestinal transit of pharmaceutical dosage forms—solutions, small pellets, and several unit forms such as nondisintegrating capsules and tablets—ranged from 3 to 4 hr, independent of the dosage form and whether the subjects were fed or fasted.[38] The gastrointestinal transit (i.e., the time

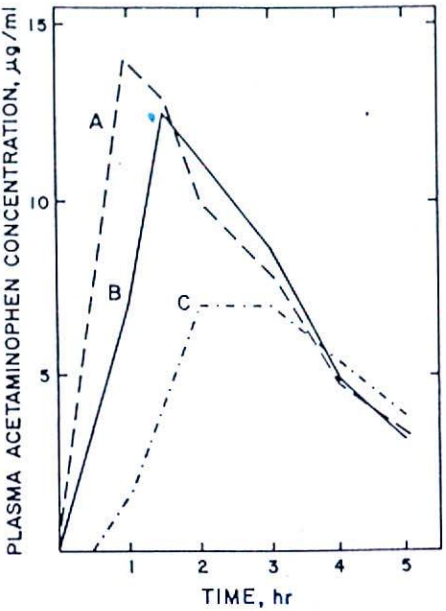

Fig. 3–7. The effects of metoclopramide (A) and propantheline (C) on acetaminophen concentrations in plasma (μg/ml) after a single oral dose of acetaminophen. The middle plot (B) shows the drug level-time curve in control subjects. Metoclopramide promotes absorption and propantheline retards absorption by affecting gastric emptying. (Data from Nimmo, J., et al.[33])

to reach the cecum after oral administration) of a constant release-rate tablet was 7.6 hr, on the average, in 4 subjects. Stomach emptying averaged 3.1 hr. Therefore, intestinal transit time was 4.5 hr.[39] The rather short residence in the small intestine has implications for the design of prolonged-release dosage forms. A product designed to release drug over a 6-hr period may demonstrate poor bioavailability if it is rapidly emptied from the stomach and the drug is poorly absorbed in the large bowel.

Propantheline and similar drugs increase small bowel transit time, whereas metoclopramide accelerates transit through the small intestine. The extent of absorption of drugs that are incompletely absorbed may be dependent on intestinal motility. Clinical studies show that propantheline increases the absorption of riboflavin by more than twofold in healthy subjects,[30] enhances the absorption of hydrochlorothiazide by about one third[40] and nitrofurantoin by about 50%,[41] and markedly increases the steady-state serum concentration of digoxin in patients on maintenance digoxin therapy.[42] In another group of patients, the concomitant administration of metoclopramide reduced the steady-state serum concentration of digoxin.[42] The effects of propantheline and metoclopramide on digoxin levels in serum are the result of changes in the extent of absorption of digoxin.

Drug absorption studies based on recovery of unchanged drug in the urine after a single oral dose indicate that the bioavailability of chlorothiazide is only about 20% after a 500 mg dose, but increases to 50% when the dose is reduced to 50 mg. These nonlinear characteristics suggest the possibility of saturable or site-specific gastrointestinal absorption, sensitive to changes in gastric emptying and intestinal transit.

To test this hypothesis, the bioavailability of chlorothiazide 500 mg was studied in fasted subjects on three different occasions, the drug given alone, given with propantheline 30 mg, or given with metoclopramide 20 mg.[43] Urinary recovery of unchanged drug was 23% of the dose when chlorothiazide was given alone, increased to 55% when propantheline was co-administered, and decreased to 13% when given with metoclopramide. The bioavailability of chlorothiazide doubled when stomach emptying rate and intestinal transit were decreased by propantheline and was cut in half when emptying and transit were accelerated by metoclopramide.

Other factors that influence motility also influence the bioavailability of certain drugs. For example, riboflavin is well absorbed in children with hypothyroidism but poorly absorbed in children with hyperthyroidism, compared with gastrointestinal absorption in healthy children.[44] Treatment of the thyroid disorder results in normalization of riboflavin absorption. These findings are consistent with the known effects of thyroid disease on intestinal transit. Accelerated intestinal transit induced by a laxative (bisacodyl) markedly decreased the azo reduction of sulfasalazine to 5-amino-salicylic acid (5-ASA) and sulfapyridine in the large bowel.[45] Urinary recovery of 5-ASA after a single dose was reduced to one-third control levels. Since 5-ASA appears to be the active component of sulfasalazine, the efficacy of sulfasalazine in the treatment of colitis may be reduced in patients with profuse diarrhea.

EFFECTS OF FOOD ON DRUG ABSORPTION

In general, gastrointestinal absorption is favored by an empty stomach, but the interaction between

food and drugs during regular treatment with oral medication is almost inevitable. Furthermore, one should not give all drugs on an empty stomach; some are irritating and should be administered with or after a meal.

There is considerable evidence that food sometimes has a marked but unpredictable effect on the rate and extent of drug absorption. Food tends to decrease the rate of stomach emptying, due to feedback mechanisms from receptors in the proximal small intestine, and often delays the rate of drug absorption. Food tends to increase gastric pH, which may increase or decrease the dissolution or chemical degradation of some drugs. Food appears to interact directly with certain drugs either to enhance or to reduce the extent of absorption. Food stimulates gastrointestinal secretions, which may facilitate the dissolution of poorly water soluble drugs. Food also stimulates hepatic blood flow, which may have implications for the bioavailability of drugs subject to first-pass hepatic metabolism.

The potential for food-drug interactions is sufficiently great that the US Food and Drug Administration now requires studies as to the effects of food on drug absorption as part of the biopharmaceutic characterization of almost every new drug intended for oral administration. This requirement is also being applied to new dosage forms of established drugs.

Welling,[46] a leading authority in this particular area of drug interactions, has reviewed the literature on the effects of food on drug absorption. In general, the absorption of drugs taken 30 min or more before a meal is not affected by food. This guideline, however, does not apply to drugs given in slowly dissolving or prolonged-release dosage forms. The potential for interaction is greatest when drugs are given with a meal or within 30 min after a meal. Food appears to have little effect on drug absorption when the drug is given 2 hr or more after a meal. In his review, Welling[46] places drug-food interactions into one of four categories: interactions resulting in unaffected, delayed, reduced, and increased drug absorption.

In most of the cases reported to date, food appears to have either little effect on drug absorption or, at worst, it decreases the rate but not the extent of drug absorption. Examples include digoxin, acetaminophen, pentobarbital sodium, various sulfonamides, and cephalexin.[47-52]

The most dramatic delays in drug absorption have been observed with enteric-coated tablets, which pass intact from the stomach to the small intestine and do not release drug until reaching the intestine. Less important effects are observed with well-dispersed dosage forms (e.g., solutions, suspensions, and rapidly disintegrating tablets and capsules), particularly when the drugs in question are water soluble. It follows that the effect of food on drug absorption may depend on the dosage form used. For example, food delays the absorption of enteric-coated aspirin tablets and digoxin tablets but has no effect on the absorption of enteric-coated aspirin granules and digoxin elixir.

Recent studies have shown that food has little effect on the absorption of enalapril,[53] an angiotensin-converting enzyme (ACE) inhibitor, and isosorbide mononitrate.[54] Enalapril is a prodrug, activated by deesterification to enalaprilat, the diacid form of the drug. The time course of serum concentrations and urinary excretion of enalaprilat after a single 40-mg oral dose of enalapril is virtually identical whether the drug is given to healthy subjects after fasting or after a standardized heavy breakfast. The oral administration of isosorbide mononitrate after a light breakfast results in a slight delay in achieving peak concentrations in plasma and a slight decrease in those concentrations, consistent with the slowing of gastric emptying, but causes no important changes in the area under the drug-concentration time curve. Similar findings have been reported for isosorbide dinitrate.[55]

The lack of effect of food on the absorption of enalapril is in contrast to the substantial effect of food on the absorption of captopril, a related drug. Singhvi et al.[56] have shown that oral administration of [^{14}C]captopril after breakfast decreases the recovery of total radioactivity in the urine from 76% (fasted state) to 49% of the administered dose. Comparing the effect of food on the absorption of enalapril and captopril, Swanson et al.[53] suggested that "oral absorption of enalapril may . . . be more complete than captopril because the sulfhydryl group of [captopril] binds to other thiol groups in food." The absorption of penicillamine, another sulfhydryl-containing drug, is reduced by about 50% when given after a meal compared with the results observed in fasting subjects.[57]

Most of the penicillins and tetracyclines, certain erythromycin preparations, lincomycin, and rifampin fall into the category of significantly reduced absorption after a meal.[58-67] Absorption of almost all tetracyclines is also markedly reduced when these drugs are taken with milk or milk products,

presumably because of an interaction with calcium resulting in a poorly soluble complex.[66] The influence of food on the absorption of antimicrobial agents is the subject of a comprehensive review.[67]

The absorption of other drugs may also be seriously impaired when given with food. For example, administration of the anticholinergic drug propantheline immediately after a meal virtually abolished its effects on salivation, suggesting a substantial decrease in absorption. In contrast, hyoscyamine suppressed salivation to the same extent whether given after a meal or to fasted subjects.[68]

Another example is hydralazine. Shepherd et al.[69] studied the effect of food on hydralazine levels and hemodynamic response in 6 patients with essential hypertension. A single oral dose of hydralazine (1 mg/kg) was given in solution after fasting and after a standardized breakfast.

Hydralazine blood levels were reduced almost 50% when the drug was given after a meal compared with the fasting state. The higher blood levels of hydralazine observed in fasted subjects produced a greater change in mean arterial pressure (MAP). Overall, a statistically significant linear correlation was observed between the percent decrease in MAP and the log of peak hydralazine concentration in blood. The authors concluded that the reduction of vasodepressor response when hydralazine is taken after breakfast suggests that patients with hypertension should take the drug at a fixed time in relation to meals.

Food dramatically affects the absorption of nifedipine.[70] After a single 10-mg dose, peak concentration was 136 ng/ml when the subjects were fasted, but only 43 ng/ml after a meal. Time to peak concentration shifted from about 1 hr to 3.5 hr. The mean AUC for nifedipine over the first 6 hr was reduced by nearly 50% when the calcium channel blocker was given after breakfast. The high C_{max} value observed in fasted subjects was associated with a large drop in blood pressure and tachycardia. Although the effects of nifedipine were less intense when taken with a meal, they remained clinically significant. Taking nifedipine after food may reduce vasodilator side effects while retaining therapeutic efficacy.

Tolbutamide taken 30 min before a meal lowers blood glucose in patients with diabetes more effectively than when it is taken with a meal.[71] This finding is clinically relevant and probably reflects both better absorption when taken in the fasted state and higher blood levels of tolbutamide at peak glucose load when it is taken 30 min before rather than with a meal.

Table 3–1. Effect of Dose on the Absorption of Riboflavin in Fasting and Nonfasting Healthy Subjects*

Dose (mg)	Percent absorbed	
	Fasting	Nonfasting
5	48	62
10	30	63
15	16	61

*Data from Levy, G., and Jusko, W.J.[7]

Increased absorption of drugs after a meal is usually rationalized in terms of the following mechanisms: (a) delayed gastric emptying causing more drug to dissolve before reaching the small intestine or a longer residence time at specific absorption sites in the small intestine; (b) increased gastrointestinal secretions (e.g., bile) improving drug solubility; (c) direct interaction and solubilization of drug by food (e.g., high-fat meals); (d) food-related increases in hepatic blood flow causing a decrease in first-pass metabolism. According to Welling,[46] "the increased absorption of riboflavin and also chlorothiazide in nonfasting subjects is probably related to nonsaturation of active absorption processes or to slow passage of drug past a gastrointestinal 'absorption window'."

The absorption of riboflavin is much greater when it is taken after a standard breakfast.[7] The data in Table 3–1 suggest that the effect of the meal increases with increasing dose of the vitamin. The substantial increase in the bioavailability of griseofulvin when given with a high-fat meal may be related to solubilization of the water-insoluble drug by lipid components of the meal and by stimulated bile secretions.[72,73]

A 20% increase in the urinary excretion of hydrochlorothiazide was found after oral administration of the drug with food compared to that observed in fasted subjects.[74] The bioavailability of chlorothiazide is doubled when taken immediately following a meal compared to that found in fasting subjects.[75] Studies in children suggest that administration of erythromycin ethylsuccinate after a meal results in a substantial improvement in bioavailability.[76]

Colburn et al.[77] recently reported that food increases the bioavailability of isotretinoin (*cis*-retinoic acid), a retinoid with low aqueous solubility indicated for the treatment of severe recalcitrant

Table 3–2. Effect of Food on the Bioavailability of Nitrofurantoin, as Determined from Urinary Excretion*

Dosage form	Percent excreted	
	Fasting	Nonfasting
Capsule (macrocrystalline)	22	40
Tablet (microcrystalline)	36	44

*Data from Bates, T.R., Sequeira, J.A., and Tembo, A.V.[79]

cystic acne. The standard dosage form of isotretinoin is a soft gelatin capsule containing the drug dispersed in lipid; bioavailability of the drug in fasted subjects is 50% or less. Increases in the bioavailability of isotretinoin of 50 to 100% were observed when the retinoid was given with a meal or 1 hr after the meal compared with the results observed in fasted subjects. The authors suggest the "stimulation of bile flow due to meal anticipation and ingestion could have enhanced the solubilization [and bioavailability] of isotretinoin."

Still greater effects of food have been reported with etretinate, another retinoid used in the treatment of psoriasis.[78] A high fat meal or two glasses of milk increased the peak concentration following a single dose of etretinate 100 mg by more than threefold and the total AUC by 3- to 4-fold.

Administration of nitrofurantoin in commercial capsules containing macrocrystalline drug or tablets containing microcrystalline drug after a standard breakfast results in more complete absorption of the antibacterial agent compared to that obtained after administration to fasting subjects.[79] The effect of food, however, is much more pronounced with the macrocrystalline form of the drug (Table 3–2). In fact, although there are substantial differences in bioavailability between the two products in fasted subjects, no significant differences were observed when the products were compared in nonfasted individuals. These findings are important because both products are recommended to be taken with food to improve gastrointestinal tolerance. The common practice of using only fasted subjects in bioavailability studies would appear to be inappropriate for drugs that are normally administered with meals.

Food increases the bioavailability of hydrochlorothiazide (HCT) and triamterene (T) from an incompletely absorbed combination product, but has no effect on the absorption of these diuretics from a well-absorbed product.[80] Studies in fasted subjects indicated that 30 to 45% of administered HCT and less than 25% of administered T was absorbed after product I, compared with 55 to 60% absorption for each drug after product II. Following administration of I with a high fat meal, the absorption of both drugs increased; the percentage of the dose of HCT and T absorbed from product I was directly related to the fat content of the meal. Food did not affect the absorption of either drug in product II.

In another study, lithium sulfate was given as a single dose in slow-release tablets to 30 healthy subjects, fasting and after a standard meal.[81] Postprandial administration produced practically no adverse effects, whereas lithium on an empty stomach caused diarrhea in about 20% of the subjects. Absorption was estimated by determining the amount of lithium excreted in the urine in a group of 10 subjects. The drug was well absorbed when given after food, but when given on an empty stomach the absorption was lower in most subjects, apparently owing to more rapid gastrointestinal passage in connection with diarrhea. The investigators propose that slow-release lithium preferably be administered after meals.

Clinical investigations convincingly demonstrate that the bioavailability of certain drugs subject to first-pass hepatic metabolism during absorption is increased after a meal. For example, administration of hydralazine following a meal results in a two- to threefold increase in bioavailability.[82]

Food has also been found to substantially increase the serum levels of propranolol and metoprolol after a single dose;[83] the propranolol data are described in Figure 3–8. Other studies have shown that the increase in propanolol bioavailability is related to the protein content of the meal.[84]

The influence of a high-protein meal on the kinetics of simultaneous iv (unlabeled) and oral (deuterated) doses of propranolol was studied in 6 healthy subjects.[85] The clearance of propranolol, as determined from the iv dose, was nearly rate-limited by hepatic blood flow. The high-protein meal increased systemic clearance from about 1.0 L/min to 1.4 L/min; bioavailability [(oral AUC × 100)/iv AUC] increased from 27% (fasting) to 45.5% (after meal).

These findings are probably the result of the well-known effect of food on splanchnic blood flow. Meals, particularly meals high in protein content, increase splanchnic blood flow transiently but substantially over fasting values. Olanoff and his colleagues,[85] found that hepatic blood flow, estimated by indocyanine green (ICG) clearance, in-

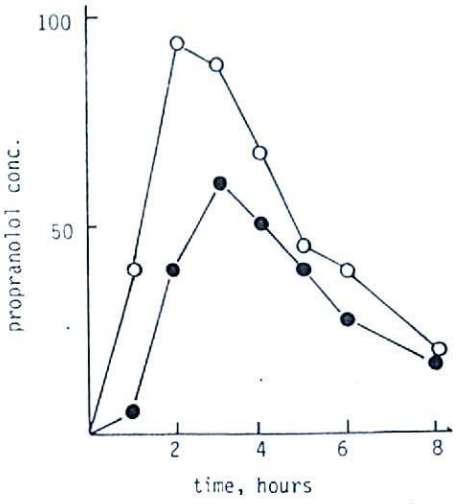

Fig. 3–8. Propranolol concentrations (ng/ml) in serum after a single oral dose to fasted (●) and fed (○) subjects. Oral administration of propranolol after a meal results in higher serum levels. (Data from Melander, A., et al.[83])

creased by 34% 60 min after the meal, from 1.7 L/min to 2.3 L/min. In theory, a transient increase in hepatic blood flow rate during absorption would allow a larger fraction of the oral dose to evade first-pass metabolism and result in an increased bioavailability.[86]

MALABSORPTION

Malabsorption may be defined as any disorder with impaired absorption of fat, carbohydrate, protein, vitamins, electrolytes, minerals, or water. Drug-induced malabsorption has been observed after administration of neomycin, phenytoin, aminosalicylate, and certain antineoplastic agents such as methotrexate.[87] 5-Fluorouracil (5-FU) damages the gastrointestinal epithelium and impairs the function of the mucosa to serve as a barrier to large polar molecules. The absorption of polyvinylpyrolidone (PVP) and tobramycin, both of which are ordinarily rather poorly absorbed, is substantially enhanced in patients receiving a course of 5-FU therapy.[88] Patients with intestinal malabsorption invariably lose weight. The most important clinical phenomena are usually those of lipid deprivation, including signs of fat-soluble vitamin (i.e., vitamins A, D, E, and K) deficiencies.

Chronic alcoholism may also lead to a leaky gut.[89] Intestinal permeability was investigated with a labeled marker in alcoholic patients and found to be significantly higher than in control subjects, even after up to 4 days of abstinence from alcohol. In several cases, increased permeability was evident up to 2 weeks after cessation of drinking. The investigators suggest that increased intestinal permeability could result in the absorption of toxic, ordinarily non-absorbable compounds (MW <5000), which might accelerate the extraintestinal tissue damage common in alcoholics.

Studies concerned with drug absorption in patients with malabsorption have been limited, and the results of such studies generally have not been remarkable. For example, the absorption of isoniazid, chloramphenicol, salicylate, and cycloserine in 10 patients with demonstrable villous atrophy, 8 of whom absorbed xylose to a limited extent, was similar to that measured in 10 healthy control subjects matched for age and sex.[90] The investigators suggest that the intestinal absorption of drugs by passive diffusion may remain largely unaltered in states in which histologic and/or abnormal results from nutrient absorption tests indicate intestinal injury.

Although some studies have shown that the absorption of digoxin is reduced in malabsorptive states,[91] others have found digoxin absorption to be normal in such patients.[92] Reduced bioavailability of digoxin in patients with malabsorption syndrome may be the result of delayed or impaired dissolution rather than a defect in the intrinsic absorption of the drug. For example, one case report showed that a patient with a radiation-induced malabsorption syndrome absorbed digoxin poorly from a tablet preparation but that substitution of digoxin elixir overcame the bioavailability problem.[93] Other investigators[94] have shown that high-dose chemotherapy [carmustine (BCNU) or cyclophosphamide] and radiation therapy decreased the absorption of digoxin by about 50%, when the drug was given in the form of a tablet. A much smaller effect, a reduction of only 15%, was noted when the drug was given as a solution inside a capsule. Chemotherapy- and radiation-induced malabsorption of digoxin can be influenced by the pharmaceutical formulation.

The difficulty of maintaining a therapeutic phenytoin concentration in a patient who developed seizures while undergoing treatment for a malignant tumor with cisplatinum, vinblastine, and bleomycin was documented by Sylvester et al.[95] Low serum levels and poor control were observed during

chemotherapy despite relatively high oral doses of phenytoin. The investigators related these findings to changes in the intestinal mucosa induced by the cytotoxic drugs, resulting in impaired absorption of phenytoin. Based on serum levels and urinary excretion data, the authors calculated that the patient absorbed only about 20% of the administered dose of phenytoin; bioavailability of phenytoin in healthy volunteers is greater than 80%.

An investigation of propranolol found that bioavailability on oral administration was similar in normal subjects and patients with untreated celiac disease.[96] Direct perfusion of the proximal jejunum, however, indicated that propranolol absorption is reduced about 70% in celiac patients compared to normal subjects. The results suggest that, ordinarily, propranolol is absorbed in the duodenum; morphologic changes in the intestine distal to the optimum absorption site have no effect on propranolol bioavailability. On the other hand, the absorption of propranolol from prolonged-release products may be impaired in patients with active celiac disease.

Concern that serum levels of cyclosporine may be inadequate in some patients prompted Atkinson et al.[97] to determine cyclosporine concentrations during oral and iv therapy in 56 patients receiving bone marrow transplants for treatment of hematologic malignancy or severe aplastic anemia. Patients with no clinical intestinal dysfunction (no vomiting or diarrhea) consistently demonstrated high serum levels after an oral dose. In contrast, patients with intestinal disease (e.g., chemoradiation enteritis, graft-versus-host disease of the intestine, or *Candida* enteritis) showed poor absorption of oral cyclosporine. Intestinal disease had no effect on serum levels of cyclosporine after iv infusions. The authors concluded that the iv infusion of cyclosporine is reliable and is the indicated route when malabsorption or intolerance of the oral preparation occurs.

Surgical resection of the small bowel can result in impaired absorption of digoxin as well as other drugs. Reduced bioavailability of digoxin was found in 5 of 9 patients who had undergone jejunal bypass surgery.[92] A strong correlation was noted between the length of jejunum remaining in continuity and the area under the digoxin concentration in serum versus time curve. The bioavailability of hydrochlorothiazide is reduced by 50% in patients who had undergone intestinal shunt operations for obesity.[98] Epileptic patients with an ileojejunal bypass receiving phenytoin are likely to require much higher oral doses to achieve adequate blood levels of the drug because absorption is only about 30% of normal.[99] In some cases, bioavailability in intestinal bypass patients may be improved by giving a more rapidly absorbed form of the drug.

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