THERAPEUTIC IMPLICATIONS OF BIOAVAILABILITY[1]

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Daniel L. Azarnoff
Departments of Medicine and Pharmacology, The University of Kansas Medical Center, Kansas City, Kansas 66103

David H. Huffman
Veterans Administration Hospital, Kansas City, Missouri 64128

There is no longer any doubt that the bioavailability of drug products may vary. Rather, the question now is whether the variation in the absorption of marketed products has any therapeutic consequences, be they production of toxic effects or reduction in therapeutic effects. These alterations in effect may be due either to changes in the rate and/or extent of absorption from the dosage form, that is, bioavailability.

Previous reviews (1–3) have concentrated on the biopharmaceutical and methodological aspects of bioavailability testing. Instead, we plan to document any therapeutic consequences that have occurred as a result of alterations in bioavailability. The expert panel on drug bioequivalence of the Office of Technology Assessment (4) recently stated there were few documented reports of clinical problems associated with bioavailability. They cautioned, however, that since the vast majority of products had not been studied, it could not a priori be stated no problems exist. The latter point should be emphasized in any review on the therapeutic implications of bioavailability.

How much change is needed in the bioavailability of a product before clinical consequences will ensue? The answer to this question will vary with the drug. Small differences in bioavailability are more likely to alter the therapeutic response of drugs that have either a steep dose-response curve or a small therapeutic-toxicity ratio. Most clinically useful drugs have relatively flat dose-response curves making it likely that only marked differences in bioavailability will alter the therapeutic

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response. Variation in bioavailability will produce a greater alteration in the therapeutic response at the lower than at the upper end of the curve (5). Bioavailability differences also become more important with drugs that have significant first-pass effects or capacity-limited absorption or metabolism.

Except for an occasional example, we do not intend to discuss variations due to chemical differences, such as salt or ester formation, since it is assumed that when a physician prescribes by generic name the pharmacist will fill the prescription with the same chemical form prescribed. Likewise, although controlled-release preparations pose significant bioavailability problems, they will not be discussed to any extent. An example of both types of problems can be seen in the studies of Svedmyr, Harthon & Lundholm (6) who demonstrated a direct relationship between the plasma concentration and pharmacological effects of nicotinic acid. Nicotinic acid given orally as regular tablets was absorbed and eliminated rapidly, resulting in large fluctuations in plasma nicotinic acid concentrations. In contrast, irregular and transitory elevations of nicotinic acid levels in the plasma occurred 5 hr after administration of an enteric coated tablet. A third preparation, pentaerythritol tetranicotinate produced moderate but consistent and prolonged levels. With equivalent doses of nicotinic acid, the acid form produced a greater free fatty acid (FFA) decrease of shorter duration as well as a more pronounced flush than the ester (7). The decrease of FFA produced by the acid form was followed by a secondary prolonged FFA elevation which was not seen with the ester. There is also evidence that the sodium salt of most barbiturates is more rapidly absorbed than the acid form (8).

ANTIBIOTICS AND CHEMOTHERAPEUTIC AGENTS

A number of investigations have been reported demonstrating varying degrees of bioavailability inequivalence of antibiotics determined by the area under the plasma concentration x time curve (AUC), peak plasma levels, or excretion in urine. However, documentation of therapeutic inequivalence is not readily available and must be inferred. Even infectious disease specialists have not decided whether the peak height or AUC is the important determinant of therapeutic efficacy. The clinical trial is not sensitive enough to determine significant differences in relative efficacy of antibiotics (9), since it is not possible in many studies to determine if the antibiotic had an effect on the course of the disease in as many as one fourth of the patients.

The purpose of chemotherapy is to hinder bacteria from multiplying for an initial period during which the animals' natural defenses are inadequate (10). After this initial period of low resistance, antibiotic therapy becomes less important as animals acquire a greater endogenous resistance to infection. With bacteriostatic agents the results of studies in mice are consistent with the hypothesis proposed by Krüger-Thiemer & Burger (11) that an adequate concentration of drug must be maintained uninterruptedly. The optimal effect with bactericidal antibiotics, however, is to be expected even if the level intermittently falls below the minimum inhibitory concentration (MIC).

The MIC range for common pathogens is 0.10–12.5 μg/ml (12–14). For a given organism, the in vitro MIC is thought to be a rough index of in vivo serum levels required for satisfactory therapeutic response (12). Comparing in vitro sensitivity of bacteria to antibiotics and the concentration of these drugs in serum with clinical results, Pullen (15) stated therapeutic blood levels should be maintained 2–5 times in vitro MIC. When the peak titer of bacteriostatic activity in serum was equal to or greater than 1:8, the infection was cured in at least 80% of the cases. The cure in patients with urinary tract infections was 90% if the titer of bacteriostatic activity in urine was equal to or greater than 1:4 (16). However, efficacy also depends on the ability of a drug to reach the site of inflammation. The peak blood level gives little indication of tissue levels, the latter often being as much as 50% less (17). If the antibiotic is rapidly excreted, the concentration in tissue fluid is particularly unpredictable. With drugs of this type, constant serum levels should be maintained to assure that tissue concentration is satisfactory (17).

The therapeutic response to isoniazid (INH) is better with a moderate dose (400 mg) than a small dose (200 mg); a single 400 mg dose is better than the same dose given as 200 mg twice a day (18). The higher peak level and better therapeutic response with the single dose are compatible with animal studies in which the best bacteriostatic and bactericidal effect is obtained when actively growing organisms are exposed to high concentrations of the drug (19). In treatment with INH alone, increasing the dosage enough to raise the peak concentrations 600% only produced a 50% improvement in therapeutic response (18). A complicating factor in the therapeutic use of INH is that some patients are slow and some fast acetylators of this drug. In one study (20), by six months, mycobacteria were still found in the sputum of only a few patients receiving INH, PAS, and intermittent streptomycin. The only significant difference among the patients occurred at 2–3 months when more than 50% of the patients with an INH blood level greater than 0.4 μg/ml at 6 hr following a dose had converted to a bacteriologically negative sputum, whereas only approximately 35% of those with levels less than 0.4 μg/ml had converted. The higher levels were found in the slow acetylators and the lower levels in the rapid acetylators.

Slow and fast acetylators may respond differently depending upon the dosage form. Controlled-release tablets given at 30 mg/kg in fast acetylators produced the same blood level as 10 mg/kg of the regular formulation in slow acetylators. The matrix preparation had a lower peak level, however, than regular INH in the slow acetylators (21). Levy & Gelber (22) in an excellent review declared 50% greater dosage is needed for fast acetylators and that the greatest efficacy with the least toxicity will be obtained when the absorption characteristics of the formulation maximizes the peak while minimizing the AUC. No difference in AUC or peak levels was observed in an evaluation of six commercial INH formulations (23). Efficacy of any INH regimen in the treatment of tuberculosis is increased by additional drugs, making it unlikely that any but the most marked bioavailability differences in INH formulation will be therapeutically significant.

In a study by Barr et al (24) brand A of tetracycline produced blood levels of 3–5 μg/ml compared to 2–3 μg/ml for brand B. The authors stated that if the MIC

were greater than 3.0 μg/ml, patients would respond better to A than B. They also found marked variation in absorption between subjects and felt the poor absorbers would do better with A than B. They also suggested that more drug remained within the gastrointestinal tract with product B, increasing the possibility of nausea, local irritation, and alteration in normal flora with overgrowth of nonsusceptible organisms. Poor and good absorbers of tetracycline have been noted by others (25) and with drugs other than antibiotics (26, 27) and may be particularly important with drugs of marginal bioavailability.

Peak plasma levels below the usually accepted 0.6 μg/ml MIC were observed with 7 of 16 lots of 250 mg oxytetracycline dosage forms given to fasting subjects. In 6 of the 7 the levels were lower than the Terramycin® standard at all four time points studied (28). Seven comparison products were also markedly lower and more variable than Terramycin at 2, 3, and 6 hr after ingestion in another study (29). Although the mean level attained with all six products being compared to Terramycin in another study (30) was above the MIC, mean levels can be misleading as demonstrated in the evaluation of 7 oxytetracycline and 2 tetracycline products marketed in Norway (31). Even though the mean value appeared satisfactory, insignificant or nondetectable levels were found in 2–3 of the 10 volunteers with some products.

Mean peak chloramphenicol plasma levels were 2.7, 6.3, 5.2, and 10.9 μg/ml and AUC 34, 61, 53, and 100% (Chloromycetin®) in a study of four formulations of this antibiotic (32). The peak levels attained by Chloromycetin ranged from 8.9–12.9 μg/ml, whereas the product with the poorest absorption was 0.7–5.1 μg/ml. This study was in healthy volunteers, but one can assume that poor therapeutic results have occurred in an occasional patient using the latter product since levels greater than 10 μg/ml are required for in vitro bacteriostasis of the majority of sensitive organisms (33, 34). However, single-dose studies may also be misleading. When Chloromycetin was compared with Amphicol, the mean concentration of chloramphenicol was greater following Chloromycetin than following Amphicol® for the initial 1–2 hr of the initial two dosing periods. With continued dosing, however, Amphicol produced higher levels than Chloromycetin (35).

Suspensions of micronized and "regular" sulfadiazine produced considerable differences in single-dose blood levels in humans (36), but again therapeutic differences can only be inferred. In another study, Van Petten et al (37) found differences in the bioavailability among four different brands of sulfadiazine and a suspension they did not consider therapeutically important. These investigators, however, stressed that at least during the loading phase of treatment in patients with a life-threatening infection, a completely and rapidly bioavailable product should be used.

Studies with griseofulvin have included correlations of bioavailability with clinical effects. One hundred and twenty-five mg tablets of griseofulvin particles with a specific surface area of 1.0 m^2/g given twice daily for 4 weeks produced a 95% cure rate in patients treated for favus. A similar dose of griseofulvin with a specific surface activity of 0.4 produced cures in only 65% ($P < 0.02$) (38). Similar results were reported by others (39) utilizing a historical comparison to the product containing the coarser material rather than a comparative trial.

Pascorbic® (PAS crystallized from a solution of ascorbic acid) supposedly has fewer gastrointestinal side effects and greater AUC than other forms of PAS permitting lower doses in the treatment of tuberculosis. However, Pentikäinen et al demonstrated that the AUC was less for Pascorbic (40) than for rapid dissolution sodium *p*-aminosalicylic acid tablets. The faster rate of absorption allows more PAS to escape acetylation by the capacity-limited enzyme activity during the first pass.

Other substances in the tablet besides active ingredients may result in therapeutic problems. Renal tubular acidosis may result from chemical changes that occur with prolonged storage of tetracycline. Degradation may be accelerated by citric acid and decreased by lactose (41), substances frequently found in dosage forms. Contaminants, such as allergenic residues in penicillin preparations, may also vary among products (42).

The concentration of nitrofurantoin in urine, not blood, is paramount in importance in the effective use of this drug. In contrast, nausea and vomiting are adverse effects which appear to be related to dose and blood level (43). Since nitrofurantoin has limited water solubility, dissolution and the rate of absorption are directly related to crystal size. Therefore, the administration of the macro crystal should decrease the peak concentration in plasma as well as the incidence of nausea and vomiting without significantly altering the concentration of the drug in the urinary tract. Less gastrointestinal intolerance was reported with the large crystal preparation in 112 patients with a previous history of this side effect. A direct comparison was not done and these complaints are quite subjective; therefore, one must wonder about the validity of the interpretation because in 287 patients without previous intolerance, no difference was observed in the incidence with regular and macronitrofurantoin (14 vs 8%). The cure rate was better than 80% with both (44). Significantly greater amounts of nitrofurantoin were found in the urine after ingestion of tablet than after a capsule formulation; however, both achieved a concentration of at least 30 μg/ml, a level that will eradicate at least 90% of most strains of *Escherichia coli* (45). This concentration was achieved within 4 hr regardless of whether the formulation consisted of regular or macro crystals (46). Two of 14 nitrofurantoin products, however, did not produce minimally acceptable concentrations of the drug in urine (47).

MacLeod et al (48) evaluated three brands of ampicillin in a crossover study in healthy volunteers. Brands B and C had 78% and 72% of the mean AUC of Brand A. The peak levels were 4.21 μg/ml for A and 3.13 and 2.87 for B and C respectively. These authors point out that the Canadian Health Protection Branch considers 80% or more of a reference standard as satisfactory (49). We cannot determine the therapeutic basis for such a standard. This statement is interesting in view of the observation that a minor modification in the fraction of dispersing agent improved the performance of Novoampicillin® (B) so that it became 17% better than Penbritin® (A) (50). Obviously, the product with the best absorption should be the reference standard since products that are incompletely absorbed have the greatest potential for erratic absorption, even within the same individual. It has been suggested that pro drug forms of ampicillin (hetacillin) could be utilized to improve ampicillin absorption since the former is hydrolyzed to ampicillin in the plasma (51).

Variable results have been reported for the bioavailability of erythromycin formulations studied in a variety of ways (single vs chronic dosing, food vs fasting, etc) (52–57). In general, the estolate is better absorbed than the stearate in single- and multiple-dosing schedules (53) and food does not appreciably alter estolate absorption whereas the absorption of the stearate is significantly reduced. In some instances, differences may be seen after a single dose such as in a study of various formulations of erythromycin stearate, 250 mg every 6 hr before meals. However, after 5 doses no differences were seen in steady state (57). Even though higher serum levels of erythromycin were obtained with the proprionate than the stearate, the authors' clinical impression was that both drugs were equally satisfactory (58). In view of the high natural cure rates of infections for which erythromycin is appropriate therapy, it is unlikely a single comparative therapeutic trial for efficacy would reveal a difference between formulations. We must keep in mind, however, that only the estolate appears to be associated with significant hepatotoxicity (59).

If a physician does not observe a satisfactory clinical response when treating patients for infections with an antibiotic he is more likely to change the antibiotic than adjust the dose upward. This approach to treatment somewhat reduces the importance of differences in bioavailability of antibiotics except in the critically ill patient.

L-DOPA

Lander (60) reported three parkinsonian patients who were well controlled with minimal nausea on capsules on L-DOPA (Synodopa®). When deterioration in the patients' condition occurred over a 3- to 5-week period, it was found that they had been changed to a tablet dosage form (Larodopa®). In one patient a return to the original satisfactory effect was obtained by increasing the dose of Larodopa from 3 to 4 g per day.

STEROIDS

Campagna et al (61) reported a patient with familial Mediterranean fever who had repeated attacks of peritonitis in which the clinical symptoms were routinely aborted by the prompt use of 20 mg prednisone taken orally daily for 2–3 days. On one occasion after taking 20 mg daily for 3 days there was no improvement. It was noted that the patient had received a generic brand of prednisone, so he was again given the brand used previously with "almost complete resolution of the clinical syndrome" within 24 hr. In another report (62), a patient adequately controlled with prednisolone tablets for arthritic pain failed to respond when a generic form was dispensed even though the patient increased the dose fourfold. His arthritis again responded when tablets of the original brand were administered.

THYROID

Lack of a clinical effect of USP thyroid tablets was noted by Catz et al (63) in a number of patients over a 9-month period. Several patients became euthyroid when

tablets of another brand were administered; the effect was substantiated by changes in the protein bound iodine (PBI). In another report, two myxedematous patients had relapses traced to substitution of enteric coated thyroid tablets for the uncoated tablets that had been prescribed (64).

DIURETICS

Tannenbaum and his associates (65) studied a fixed ratio combination of hydrochlorothiazide and triamterene formulated in tablets and capsules with quite different pharmaceutical ingredients. Absorption of both diuretics was twofold greater from the tablet than from the capsule. The tablets consistently produced an effect on sodium excretion that was greater than the capsule ($P < 0.01$). Although the 12 hr sodium excretion was greater following the tablets, the rapid onset and marked effect of this dosage form invoked compensatory mechanisms for conservation of the sodium. A similar situation was not observed with capsules. As a result, the 24 hr naturetic effect of the two dosage forms was essentially the same.

In 1963, Shaldon et al (66) demonstrated in eight patients with stable ascites secondary to cirrhosis of the liver controlled by administration of chlorothiazide and spironolactone (Aldactone®) that a preparation of smaller particles (Aldactone A®) was effective at one fourth the dose. Plasma levels and excretion in the urine of the major metabolite, canrenone, were also equivalent at the reduced dose. The importance of particle size was further defined in a study in dogs by utilizing the appearance of canrenone in blood as well as the ratio of sodium/potassium excreted in urine (67). These studies make it obvious that dose-related therapeutic and adverse effects may be affected by significant differences in bioavailability of products of spironolactone.

Potassium supplementation is frequently required with chronic diuretic use. Tablets of KCl have been associated with more than 300 cases of severe ulceration, hemorrhage, and stenosis of the small bowel thought to be due to the local effect of a high concentration of KCl in the bowel following release from the tablet (68). Solutions of KCl are available but patient compliance is poor because of the unpleasant taste and minor gastrointestinal complaints. Solutions of potassium gluconate, bicarbonate, citrate, and acetate taste better, but chloride is essential for effective supplementation of potassium (69). Ben-Ishay & Engleman (70) compared a single 40 meq dose of a 10% KCl solution and a slow-release tablet (Slow-K) in ten normal subjects. The amount of K^+ in the urine increased sooner and to a greater peak with the solution. However, after four days of administration no difference in net potassium excretion in urine was noted following equivalent doses. Although much better tolerated, under unusual circumstances, an occasional case of stenosis still occurs with the slow-release preparations (71).

ANTICONVULSANTS

Unusual central nervous system symptoms in patients receiving one brand of phenytoin sodium (Dilantin®) were described in letters to the *Medical Journal of Australia* in 1968. The symptoms occurred primarily in patients stabilized on a high dose of this drug product (72–75). In 87% of the patients, plasma phenytoin levels were

above the therapeutic range and reduction of the dose ameliorated the symptoms (76). Subsequently, it was determined that the excipient in the capsules had been changed from $CaSO_4$ dihydrate to lactose and the amount of magnesium silicate and magnesium stearate increased slightly. Direct evidence for the increased absorption of phenytoin from the new formulation was obtained by measuring blood levels in a crossover study of 13 subjects (77). This study further demonstrated an increased fecal loss of phenytoin, apparently secondary to decreased solubility of phenytoin in the presence of calcium sulfate.

ANTI-INFLAMMATORY DRUGS

Katz and co-workers (78) carried out an extensive therapeutic trial with indomethacin in 97 patients with rheumatoid arthritis and other rheumatoid disorders. They noted a 37% incidence of adverse reactions including six patients who developed peptic ulcers. Doses of 100–400 mg of hard-pressed tablets later shown to have variable and erratic absorption were used in this study. Subsequent studies were done with a 25 mg capsule containing ultrafine milled powder. This formulation was associated with a more uniform rate of absorption and more predictable blood levels (79). Doses of 75–150 mg of this preparation produced 61% improvement compared to 42% in the previous high-dose studies. The adverse reactions decreased from 37 to 12% and no serious complications occurred.

The bioavailability of nine brands of phenylbutazone was studied in 10 healthy volunteers given a light, standard breakfast 1–1.5 hr before dosing (80). The percent absorption relative to an oral solution varied from 56.8 (Brand E) to 100.6 (Brand A). Based on theoretical considerations, the authors concluded that with chronic dosing all brands would achieve peak levels between 94 and 155 μg/ml by 36 hr. Brand E was the only brand significantly lower than A. Because of induction of its own metabolism, Burns et al (81) found that the limit of the plasma concentration with chronic dosing is 60–150 μg/ml. Five brands did not achieve peak levels until 4–8 hr so that the first dose of these preparations might not relieve the patients' discomfort satisfactorily. Otherwise, all tablets tested produced blood levels considered within the therapeutic range. Two of 23 brands of phenylbutazone tablets resulted in what the authors considered inadequate blood levels; this interpretation is questionable and based on only two healthy volunteers. Therefore, it is impossible to extrapolate the results to therapeutic response (82).

In 1963, a series of letters to the editor appeared in the *Canadian Medical Association Journal* reporting experiences with diabetic patients whose blood sugars were controlled by brand name tolbutamide preparations. A change to generic tolbutamide preparations was associated with hyperglycemia (83, 84). As a result, doubt was cast on the efficacy of three brands of tolbutamide sold in Canada by nonproprietary name. To evaluate this problem, two brand and three generic products were studied in a crossover design in 22 diabetic patients given 1–2 g tolbutamide per day (85). Fasting, midmorning and midafternnon blood sugar and tolbutamide levels were measured in addition to excretion of carboxytolbutamide in a 24 hr urine. The only difference observed was better control of the fasting blood

sugar by one brand. No clinical differences were observed by the investigators. It must be remembered that secondary failures (8% per year) as well as temporary resistance to tolbutamide occur not uncommonly in response to a variety of emotional and physical stresses (86).

Variation in tolbutamide bioavailability caused by minor pharmaceutic variation has been demonstrated by Varley (87). Ten healthy and 9 diabetic volunteers were studied in a double-blind, crossover study comparing a tablet of Orinase® with a similar tolbutamide tablet containing half as much Vee Gum®. The 8 hr AUC for Orinase was 3.57 times greater than the other tolbutamide tablet ($P < 0.001$). The pharmacological effect determined as the AUC of blood sugar lowering was 2.09 times greater with Orinase, the difference in effect occurring, however, only in the first 3 of the 8 hr. It must be remembered the tablets with inadequate bioavailability were not a marketed product.

ANALGESIA

Two dosage forms of naproxen suppositories were found essentially the same except for the rate of absorption, which may be important if rapid analgesia is required (88). Phenacetin produces central nervous system side effects in volunteers, which were well correlated with phenacetin blood levels and bioavailability of the preparation. The adverse effects came on rapidly, primarily after administration of a fine suspension (less than 75 μ) of the drug and seldom after the preparations containing particles greater than 150 μ (89).

No difference was found in buffered and unbuffered aspirin in either efficacy or gastrointestinal tolerance in 160 patients receiving the products acutely and chronically (90). Similar results were obtained in a study of 1434 patients (91). A soluble form of aspirin (Alka Seltzer®) did cause less gastrointestinal bleeding than plain aspirin (92). Physiological differences secondary to variation in aspirin formulations were found by Pfeiffer et al (93) utilizing monopolar-integrated electroencephalographic changes to quantitate effect.

It is difficult to evaluate the efficacy of drugs that influence the central nervous system since even the color of the product may influence the effect (94). The evaluation process is further complicated by the presence of slow and fast absorbers of acetaminophen (26) and aspirin (27). Bioavailability differences between acetaminophen products were only detected in the slow absorbers (95).

TOPICAL PREPARATIONS

Bioavailability problems are also likely with topical preparations. Aware that there is a good correlation between blanching and alleviation of inflammation (96), Woodford & Barry (97) tested 30 proprietary hydrophylic topical corticosteroid preparations for their ability to produce blanching in 10 volunteers. All the preparations were within 90% of each other except for one with 78% and one with 54% effectiveness. In 50 patients with chronic bilateral inflammatory dermatoses (eczema and psoriasis) a solution of fluocinolone acetonide in propylene glycol dispersed in

soft paraffin (A) was compared to a microcrystalline powder (B) suspended in soft paraffin (98). In 32% of the patients with eczema there was no difference between the two preparations, whereas 82% of the remaining patients had better results with A compared to 12% with B ($P < 0.02$). Fifty-two percent of patients with psoriasis did equally well with A or B. However, 36% of the remaining patients did better with A compared to 12% with B ($P < 0.15$). Overall there was no difference in 42% of the patients. In the remaining patients 79% did better with A than B ($P < 0.005$).

CARDIAC GLYCOSIDES

Following the report by Lindenbaum et al (99) of variation in the bioavailability of digoxin tablets from different manufacturers and even different lots of the same manufacturer, there have been other studies demonstrating that digoxin tablets are incompletely (20–75%) and variably absorbed (100–108). A good correlation exists between the serum digoxin concentration and the patient's clinical response to the drug (109). Since a narrow margin exists between the therapeutic and toxic digoxin levels (110–112), differences in bioavailability may have significant therapeutic consequences.

A prime example of the therapeutic consequences of variation in bioavailability of digoxin tablets occurred in the United Kingdom where in 1969 a "minor change" in the manufacturing process of Lanoxin® was installed. During the latter half of 1971 a number of patients with atrial fibrillation developed either congestive heart failure or a rapid ventricular response despite continuing the same dose of Lanoxin (113–116), which previously controlled their cardiac disorders satisfactorily (117). Considerable variation in absorption from the "new" and "old" tablets was manifested by an unpredictable increase in digoxin levels when the patients were changed from one to the other (114). The experience in Great Britain leaves little doubt that changes in bioavailability of digoxin tablets result in important alterations in the therapeutic response to digoxin (116).

The bioavailability of digoxin is also altered by certain types of malabsorption (118) and the coadministration of other drugs (119), particularly those that affect gastrointestinal motility (120). The administration of either metaclopramide and propantheline significantly alter the absorption of digoxin tablets; the altered absorption of digoxin secondary to the latter drugs is not significantly affected when the digoxin is given as a solution or a rapidly dissolving tablet (121). Similarly, Jusko et al (122) reported a low serum digoxin concentration in a patient maintained on digoxin tablets following radiation therapy to the small bowel. The concentration was increased to the therapeutic range when the same dose of digoxin was administered orally as an elixir.

ANTICOAGULANTS

Bleeding during treatment with oral coumarin anticoagulants is directly related to an excessive decrease in prothrombin activity (123) or to inhibition of platelet aggregation in an anticoagulated patient. Because of the poor solubility of dicumarol

in water, formulation changes may markedly affect the therapeutic effect as measured by the prothrombin time. Both hemorrhage and ineffectiveness of previously satisfactory doses have occurred in some patients. Simply adding filler to change the tablet size to make it easier to break in half led to bioavailability problems due to differences in the dispersion and thus the rate of dissolution of the drug (124). Even when comparing one manufacturer's product it was found that five 5 mg warfarin sodium tablets were absorbed twice as fast as one 25 mg tablet; the latter tablet was only 80% absorbed compared to the five smaller tablets (125). However, bioavailability problems are less likely with warfarin sodium than with dicumarol because of the significant water solubility and long plasma elimination $T_{1/2}$ of the former.

VITAMINS

There are several reports of marked differences in the bioavailability of water- and fat-soluble vitamins (126–128). The therapeutic importance of such differences is difficult to assess since vitamins are usually taken in great excess of actual requirements and by individuals who are not actually deficient.

We have limited this review primarily to single-entity products, to similar chemical entities, and to similar-dosage forms. Controlled-release dosage forms are a special problem. We conclude that documentation of therapeutic consequences of differences in bioavailability have been few. However, a significant number of studies in healthy volunteers clearly demonstrate that the potential for alteration of therapeutic effect due to variation in bioavailability is quite significant. The lack of documentation of therapeutic alterations may be due to (*a*) the flat dose-response curve of many therapeutic agents, (*b*) physicians' lack of awareness of the potential effects of alterations in bioavailability, (*c*) the small number of patients any physician sees using one drug product, (*d*) the similarity of toxic effects of some drugs and the disease being treated (e.g. cardiac arrhythmias due to myocardial disease and digitalis), (*e*) concomitant use of more than one drug or mode of treatment (e.g. digitalis and diuretics for congestive heart failure), and (*f*) use of specially prepared, nonmarketed products in healthy volunteers in many of the studies designed to show differences.

The potential for therapeutic inequivalence of dosage forms due to variation in bioavailability emphasizes the need for compendial standards to minimize the problem.

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