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Bioavailability of Digoxin Tablets*

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UNTIL recently investigators who have studied the absorption of digoxin in man have utilized the tritium-labeled glycoside given in solution by mouth rather than in tablet form. The absorption of digoxin from such solutions by human subjects has been estimated to be approximately 85% by Doherty *et al.* (9), though other investigators also studying the absorption of digoxin solutions have concluded that this figure was too high (3) or too low (16). The recent availability of radioimmunoassay procedures for measurement of digoxin concentrations in serum (6) and urine (16, 23) has made it possible to study the bioavailability of digoxin tablets in normal human subjects and in patients.

Absorption of Digoxin from Tablet Formulations

We have measured serum digoxin concentrations by a radioimmunoassay method (7, 25) in 25 healthy physicians and laboratory technicians, ages 22 to 32, after the ingestion in the fasting state of two 0.25-mg tablets from a single lot of digoxin (Burroughs Wellcome, Lanoxin, lot Z-180). The mean levels achieved up to 6 hr after oral administration are shown in figure 1. The shape of the acute serum absorption curves resembles that reported by Doherty *et al.* (9, 10) and Marcus *et al.* (22) who used solutions of tritiated digoxin, and by White *et al.* who used methods similar to ours in eight subjects taking digoxin tablets (27). The standard deviations shown in figure 1 indicate a wide intersubject variation in this healthy population group. There was a 3-fold variation in peak serum concentration achieved (range 0.96 to 2.80 ng/ml, mean 1.62 ng/ml). The time at which the peak value was attained varied from ½ to 2 hr after oral ingestion of the tablets. Variability was also noted in the eight subjects reported by White *et al.* (27). Individual volunteers tested on more than one occasion with the same lot of digoxin showed little (fig. 2, subjects J. D., J. S., and T. W.) or marked (fig. 2, subject S. S.) intrasubject variation. While many factors, such as rate of gastric emptying, size of tissue digoxin space, and metabolic handling of the glycoside will undoubtedly affect serum levels after ingestion of the drug, differences in rate or extent of absorption or both may also be contributory. A wide range of fecal excretion of isotope was reported by previous investigators who used tritiated digoxin (3, 10, 22).

To determine whether digoxin was incompletely absorbed in tablet form in normal individuals, serum and urinary digoxin levels recently were compared after oral administration of a solution available for therapeutic purposes (Burroughs Wellcome Lanoxin pediatric elixir, containing 10% alcohol and 0.1% methylparaben as preservative, lot 962 B) or of a lot of digoxin tablets (Burroughs Wellcome Lanoxin, lot Z-180). The particular lot of tablets chosen for study previously had been shown to be relatively well absorbed compared to other digoxin products (18). Crossover studies were performed in five normal physician volunteers, ages 26 to 32. Each subject served as his own

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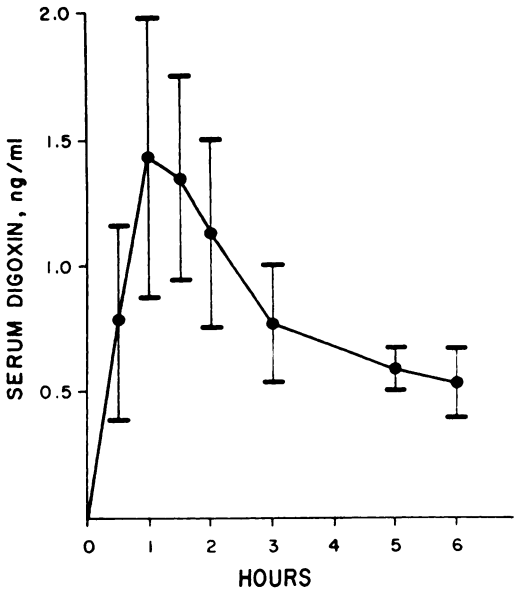

FIG. 1. Serum digoxin concentrations (mean ± 1 S.D.) after a single 0.5 mg oral dose of Burroughs-Wellcome digoxin (lot Z-180) in 25 normal subjects. (Serum at 6 hr was only obtained from nine subjects).

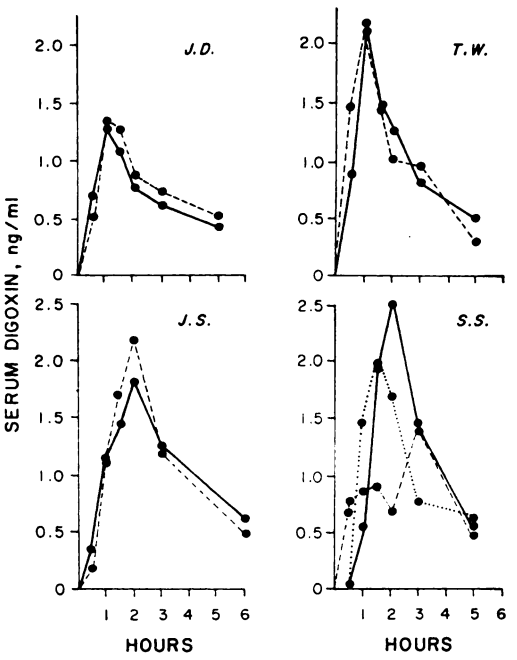

FIG. 2. Serum digoxin concentrations after the oral ingestion of 0.5 mg of Burroughs-Wellcome digoxin (lot Z-180) on two occasions in three subjects and on three occasions in a fourth (S. S., lower right).

control, ingesting 0.5 mg of digoxin elixir or tablets in random order on two occasions separated by 14 days. In every individual the peak serum digoxin concentration achieved was higher with the elixir, though the time at which peak levels were reached was similar. The mean serum digoxin concentrations (fig. 3) differed significantly at 1 and 3 hr ($P < .02$ and $< .05$, respectively). The areas under the curves obtained after ingestion of the tablets averaged 62% (range 47% to 77%) of those after administration of the elixir ($P < .02$).

In eight normal physician volunteers similarly studied on two occasions after the ingestion in random order of 0.5 mg of the tablet, or of the elixir, total 24-hr urinary digoxin excretion was measured. Multiple dilutions of urine were tested by a modification of the radioimmunoassay method with pooled normal human urine rather than plasma in the standard curve (23). The urinary digoxin excretion after the tablet was less in each subject (fig. 4) and averaged 59% (range 34% to 80%) of the values obtained after the elixir. These differences were highly significant ($P < .001$) and strongly suggest that digoxin in tablet form is incompletely and variably absorbed by normal human subjects. The findings are consistent with those of Huffman and Azarnoff (16), who compared 10-day urinary digoxin excretion after single doses of Burroughs Wellcome tablets or an oral digoxin solution in crossover studies in four healthy subjects. By this method the average absorption of the tablet form of digoxin in these individuals was estimated to be 75% (16).

Variation in Bioavailability of Digoxin Products

With an agent that is incompletely absorbed in tablet form, the potential for variation in the amount of drug absorbed from different formulations may be great. In studies conducted by our group during the past 2 years, we have compared the relative bioavailability of several digoxin products com-

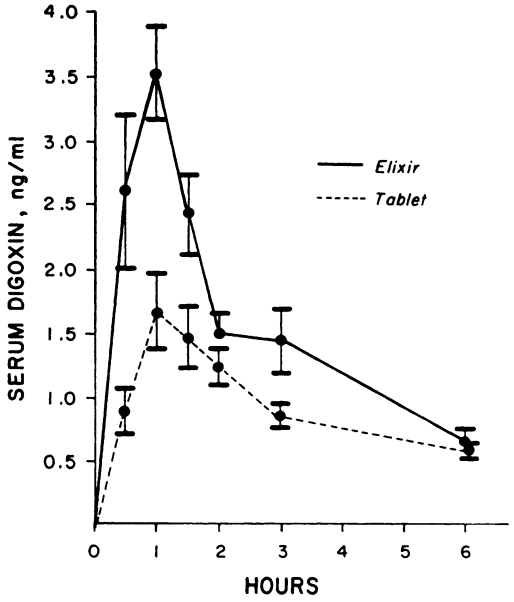

FIG. 3. Serum digoxin concentrations (mean ± 1 S.E.) after 0.5 mg oral doses of Burroughs-Wellcome digoxin in elixir and tablet form in five normal subjects.

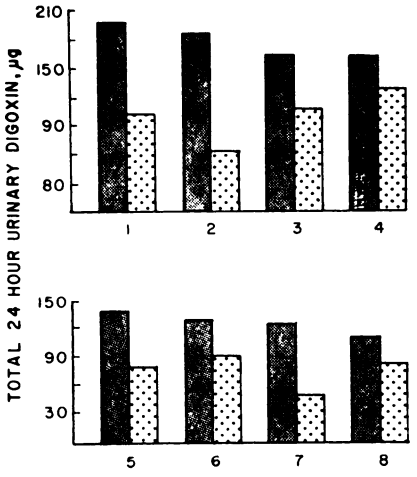

FIG. 4. Total 24-hr urinary digoxin excretion in eight normal subjects after 0.5 mg of Burroughs-Wellcome digoxin in elixir (solid bars) and tablet form (dotted bars). The mean digoxin excretion (±1 S.D.) after the elixir was 151 ± 31 μg, and after the tablet was 82 ± 26 μg ($P < .001$).

mercially available for patient use in the New York City area. Tablets of product "A" were from the same lot of Burroughs Wellcome digoxin (Z-180) also used in the investigations summarized above (figs. 1–4). This was chosen as a reference standard since this manufacturer was responsible for the original development of digoxin and this product has been widely used in past studies of dosage requirements for the glycoside. Other preparations tested were selected because of apparent therapeutic ineffectiveness (*i.e.*, high maintenance requirements associated with serum digoxin concentrations below or at the lower end of the usual therapeutic range) documented on the wards of Harlem Hospital Center (products B_2, C, and D) or anecdotal reports of inadequate therapeutic effect received from outside physicians (preparation E).

In the first study, serum digoxin concentrations ½ to 5 hr after the oral administration of 0.5 mg of products A, B_2, and C were measured in crossover studies in four healthy physicians (18). In addition, another lot from manufacturer B (designated B_1) was also tested. Marked differences were noted between A and B_1, on the one hand, and B_2 and C, on the other, in peak levels achieved, serum concentrations at various points in time (fig. 5), and the plotted areas under the absorption curves (18). Product C was of particular interest since it was absorbed poorly by three of the subjects studied, and relatively well by the fourth (fig. 6). Significant differences were also noted between lots B_1 and B_2 obtained from the same manufacturer (18).

In more recent studies (19), significant impairment in the bioavailability of products D and E, again as compared with A, has been demonstrated (figs. 7 and 8). In work currently in progress, tablets from a second lot of digoxin marketed by manufacturer E have been shown to be as well absorbed as those from a lot of Burroughs Wellcome digoxin, again indicating variation in bioavailability between different batches of glycoside produced by a single manufacturer.[1]

Inspection of the serum absorption curves

[1] Preibisz, J. J., Lindenbaum, J. and Butler, V. P., Jr.: To be published.

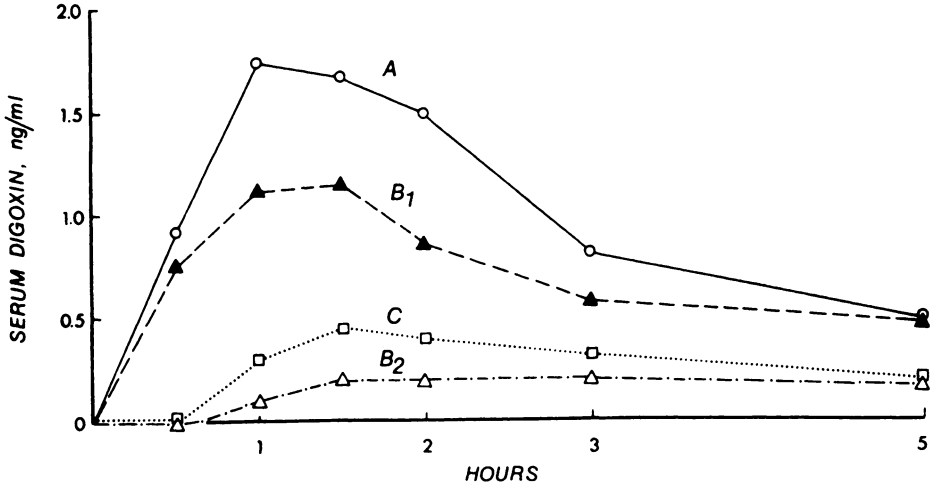

FIG. 5. Mean serum digoxin concentrations after oral administration of digoxin products A (Burroughs-Wellcome, lot Z-180), B_1 and B_2 (American Pharmaceutical Co. lots B15703 and OA 12933), and C (Davis-Edwards Co., lot 24938) to four normal subjects. Serum levels after A differed significantly (P less than 0.05 or less) from those after B_2 and C at every point on the curve after 0 hr except at 3 hr. Serum levels after B_1 significantly exceeded those after B_2 at every point except 3 hr and those after C at ½, 1, and 5 hr. A did not differ significantly from B_1, or B_2 from C, at any point. [Reproduced from Lindenbaum *et al.* (18)].

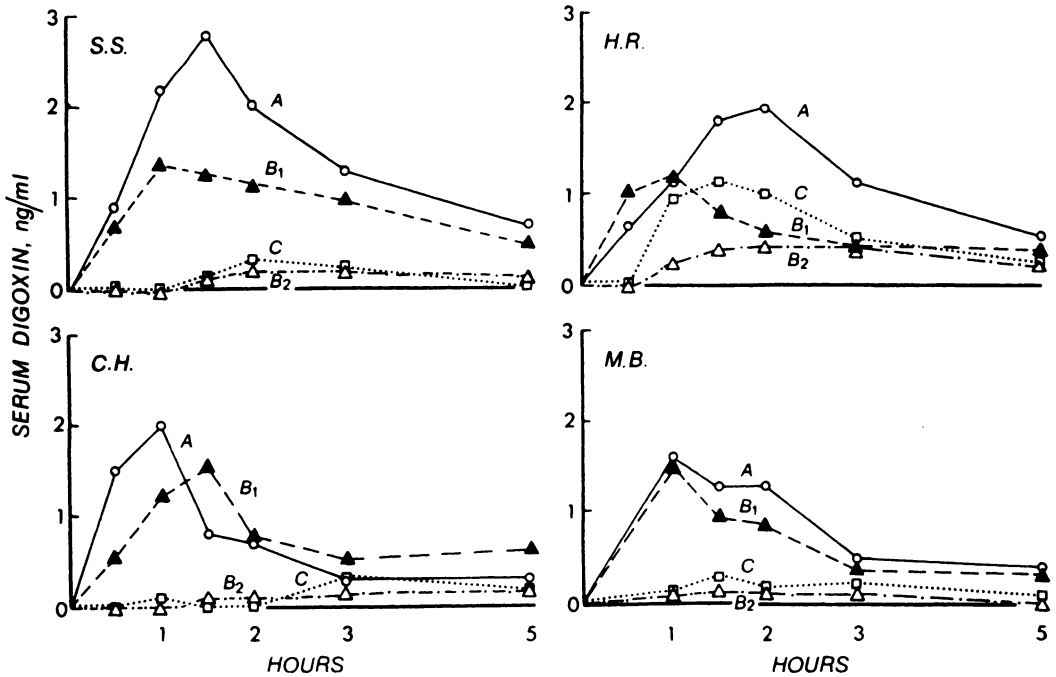

FIG. 6. Individual absorption curves after digoxin products A, B_1, B_2, and C in four normal subjects. Serum digoxin levels at ½ hr were not obtained in M. B. [Reproduced from Lindenbaum *et al.* (18)].

obtained with various products exhibiting decreased bioavailability reveals two different pharmacokinetic patterns. In one, exemplified by product D (fig. 7), the rate of absorption appears to be similar to that of A, with a peak blood level usually attained within an hour of oral administration. In contrast, products B_2, C, (figs. 5 and 6) and

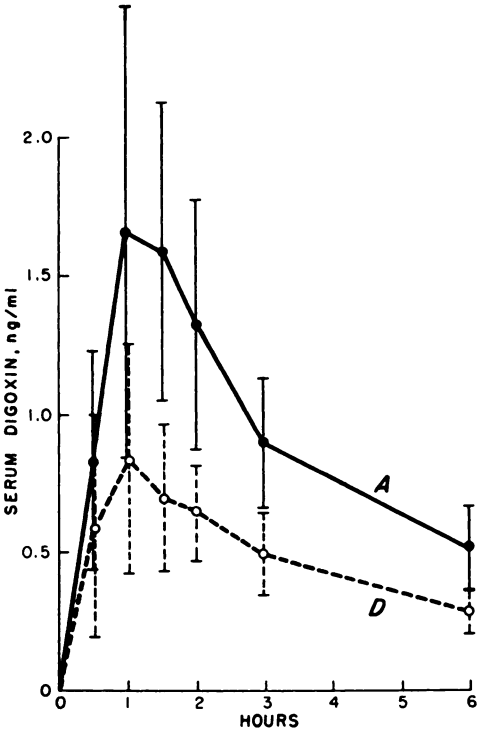

FIG. 7. Mean (±1 S.D.) serum digoxin concentrations after single 0.5-mg oral doses of products A (Burroughs-Wellcome, lot Z-180) and D (Fougera, lot 1979) in eight normal physician volunteers. Serum levels were significantly higher after product A at all times except at ½ hr ($P < .02$ at 1 hr, $P < .005$ at all subsequent points). The mean peak concentration after A (1.93 ± 0.64 ng/ml) was twice that after D (0.96 ± 0.28 ng/ml, $P < .005$) though the mean time to reach peak serum levels was similar (1.3 and 1.4 hr, respectively). The areas under the curves differed significantly ($P < .001$). [Reproduced from Lindenbaum *et al.* (19)].

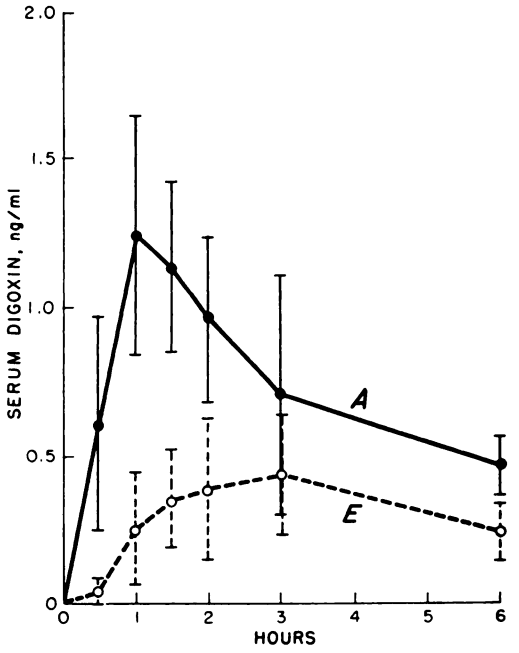

FIG. 8. Mean (±1 S.D.) serum digoxin concentrations after single 0.5-mg oral doses of products A (Burroughs-Wellcome, lot Z-180) and E (Purepac, lot 18919) in six normal subjects. The differences were significant ($P < .05$) at every point on the curve except at 3 hr. Areas under the curves differed significantly ($P < .005$). The mean peak level after A (1.34 ± 0.38 ng/ml) was almost three times that after E (0.48 ± 0.10 ng/ml, $P < .001$). The mean time to reach peak concentrations after E was delayed (A, 1.5 hr; E, 3 hr). [Reproduced from Lindenbaum *et al.* (19)].

E (fig. 8) show delayed absorption, reaching peak concentrations approximately 2 hr after A.

Several groups of European and American investigators recently have also reported variation in bioavailabiilty of different digoxin products (4, 5, 20, 24). Another group found that serum absorption curves obtained after three European digoxin products were essentially equivalent (15). Differences in the bioavailability of different lots of digoxin from a single English manufacturer have been reported (26, 28), and denied (21). It has been suggested that pronounced discrepancies in bioavailability between glycoside preparations will be manifested only in selected patients, for undetermined reasons (24).

Variation in Tablet Content Uniformity

Thus major differences in bioavailability exist between preparations of digoxin currently available for use in patients. This variation in absorption must be distinguished from a separate problem in the formulation of digoxin products, that of individual tablet content uniformity, *i.e.*, variability beyond U.S.P. established limits in the chemical potency *in vitro* of single tablets within the same lot. In 1970 the Food and Drug Administration systematically studied the digoxin preparations on the American market and found such variation in 47% of the lots

tested, after which the F.D.A. took appropriate regulatory action (11). One of the formulations shown to be poorly absorbed in our human subjects (product B_2) failed to meet U.S.P. standards for tablet content uniformity. However, content uniformity analyses of 10 individual tablets from the same lots of products C, D, and E (as well as A) used in our bioavailability studies were performed by the National Center for Drug Analysis, F.D.A.,[2] and each of these preparations met U.S.P. requirements. Thus the impairment of bioavailability of these products cannot be attributed to decreased chemical digoxin content (19).

Urinary Digoxin Excretion as a Measure of Bioavailability

Since serum glycoside concentrations were only measured for 5 to 6 hr in our previous bioavailability studies, it can be argued that absorption was not complete by that time (16), and that the differences noted among digoxin products reflected primarily variation in the rate rather than the extent of absorption. Since digoxin is primarily excreted in the urine, estimation of urinary digoxin should be a valid reflection of bioavailability (16, 19). If complete urine collections can be obtained from subjects with normal renal function, urinary measurements may have certain advantages over the serum absorption curves. If collections are extended for periods of 24 hr or more, differences in rate of absorption should be minimized, and a better reflection of total amount of drug absorbed obtained. The use of urinary digoxin measurements would also require decreased numbers of laboratory determinations and less expense for compensation of volunteer subjects. In six normal individuals who took 0.5 mg of products A and D in crossover studies, urinary excretion of digoxin (fig. 9) was measured (19). The mean total 24-hr urinary digoxin after A (104 ± 13 μg) was substantially higher than that after D (59 ± 8.5 μg, $P < .001$). There was a significant correlation between the areas under the serum absorption curves and the urinary glycoside levels ($r = 0.718$, $n = 12$, $P < 0.01$) (19).

The mean serum half-life of digoxin after chronic oral digitalization with Burroughs Wellcome tablets in six normal subjects studied in our laboratory was 32 hr, a figure that agrees well with that of 33.8 hr reported by Doherty *et al.* with tritiated digoxin (9). Thus a 24-hr urinary collection period is less than a single drug half-life and considerable glycoside excretion by this route continues for several subsequent days (9, 16, 22). Incontrovertible proof of impaired bioavailability, therefore, would require evidence of decreased "steady state" serum levels in chronically digitalized subjects, or complete urine collections extending beyond several drug half-lives after a single dose. Studies currently in progress by our group indicate an excellent correlation between "acute" serum digoxin curves, 24-hr urinary excretion after single doses, and serum and urinary levels after 10 days of daily drug dosage with products A, D, and E.[1] These findings are in accord with previous clinical observations of reduced therapeutic effectiveness of the agents with impaired acute bioavailability. They point to the continued usefulness of serum and urinary digoxin measurements after single doses as a method of study of bioavailability of this glycoside. We believe that the 24-hr urinary digoxin excretion may prove to be a practical and useful screening test for bioavailability.

Some Remaining Problems

The mechanisms underlying the differences in bioavailability of digoxin products remain to be determined. One reasonable working hypothesis is that they are related to differences in the rate at which digoxin molecules become dissolved in gastrointestinal fluids. Differences in dissolution rate *in vitro* of two formulations of English Burroughs Wellcome digoxin have been reported (13, 21). After oral ingestion of the more rapidly dissolving tablets, considerably

[2] Courtesy of Dr. Arthur W. Steers.

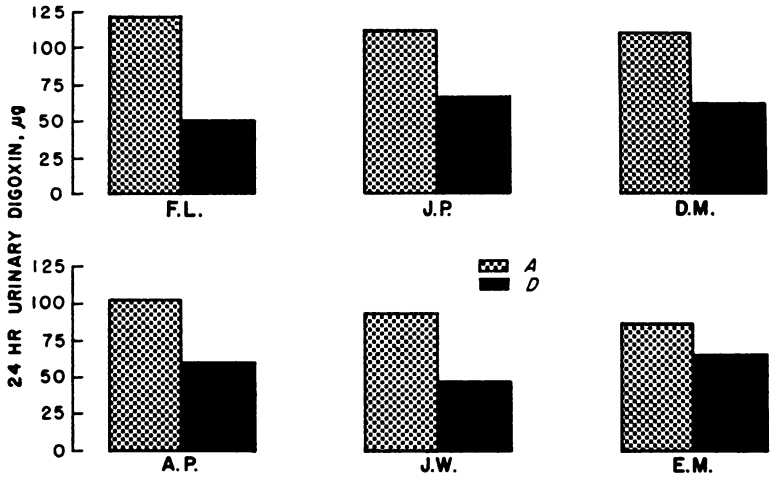

FIG. 9. Total 24-hr urinary digoxin excretion in six normal subjects who took 0.5 mg of products A and D on separate occasions 2 weeks apart in random order. In every volunteer more digoxin was recovered in the urine after A than D. [Reproduced from Lindenbaum *et al.* (19)].

higher peak serum levels were obtained (21, 26). Two digoxin preparations available in Sweden which differed in dissolution rate *in vitro* showed parallel differences in steady state levels after chronic administration in three out of four human subjects studied (4). A digoxin product that was poorly absorbed in a single subject was reported to have a larger particle size than a better absorbed preparation (24).

Shaw *et al* (24) found the absorption of English brands of digoxin that showed poor bioavailability in some patients was enhanced markedly when the material was crushed and given in capsule form (24). Individual tablets of products A, D, and E were ground to a fine powder with a mortar and pestle in our laboratory and the powders administered in gelatin capsules to two normal physician subjects. Superior bioavailability of preparation A was again apparent in both subjects (fig. 10).

The digoxin particle size after crushing the tablets was not measured in our study or that of Shaw *et al.* (24). Further investigation of the relationships between behavior of various digoxin products *in vitro* and *in vivo.* as well as attempts to develop a better standardized method for measuring digoxin dissolution rate, are currently in progress in several lab-

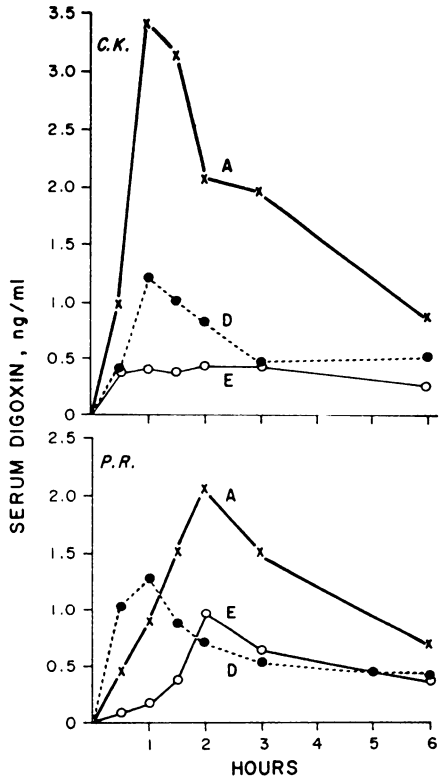

FIG. 10. Serum digoxin concentrations in two normal physician subjects who ingested capsules containing 0.5 mg of products A, D, and E after the tablets had been crushed into a powdered form. Twenty-four-hour urinary excretion of digoxin (not shown) was also much greater after A than after D and E.

oratories. If differences in absorption could be clearly related to some measurement *in vitro*, the solution to the problem of variation in digoxin bioavailability obviously would be facilitated greatly. Preliminary data indicate a striking correlation between dissolution rate and serum digoxin levels after a single dose of 11 different digoxin products of varying bioavailability.[3]

In the meantime, the established discrepancies in the absorption of digoxin products currently available represent a hazard to the patient and may contribute to clinical variation in both the therapeutic and toxic effects of the glycoside. We have, therefore, repeatedly urged that governmental regulatory action in this area be taken (18, 19).

The establishment of bioavailability standards for digoxin products presents a complex problem, in view of the demonstration by Huffman and Azarnoff (16) and ourselves (figs. 3 and 4) that even Burroughs Wellcome tablets are incompletely absorbed. The development of a tablet that is 100% absorbed compared to a solution of the glycoside, if such were possible, might be undesirable since widely used, time honored digoxin dosage schedules have been based on work with Burroughs Wellcome tablets and would have to be revised.

Other Factors Affecting the Absorption of Digoxin Tablets

Food

White *et al.* (27) compared plasma digoxin concentrations when Burroughs Wellcome tablets were taken in single or multiple doses in the fasting state and after breakfast. When single doses of the drug were ingested after food, peak serum concentrations were considerably decreased, but "plateau levels" 6 to 8 hr after glycoside administration did not differ significantly (27). Mean steady state concentrations after chronic administration were slightly lower when digoxin was taken after breakfast, but not significantly so (27). In a study of two digoxin formulations that were shown to be absorbed at different rates in the fasting state, the chronic administration of the tablets with food may have minimized these differences as reflected by steady state serum levels (21).

[3] Cresswell, R. and Lindenbaum J.: Unpublished observations.

Malabsorption States

Heizer *et al.* (14) reported mean steady state serum digoxin concentrations to be lower in a group of nine patients with various malabsorption syndromes than in a control population with congestive heart failure.

Drug-drug Interactions

The administration of single doses of neomycin sulfate along with 0.5 mg of Burroughs Wellcome digoxin resulted in a 5-fold depression of serum digoxin concentrations at 1 hr compared to the same dose of the glycoside taken alone (17). Steady state serum levels were also significantly reduced by the concomitant ingestion of 2 to 4 g of neomycin daily along with digoxin. Although neomycin is well known to precipitate bile salts out of solution (12), it does not have this effect on the solubility of digoxin (17), and it is likely that the antibiotic affects the mucosal absorption of the glycoside.

Anion exchange resins have been shown to bind digoxin *in vitro* (2, 8) and are currently under evaluation as a means of treating digoxin intoxication *via* interference with the enterohepatic circulation of the glycoside (2). The chronic co-administration of steroid-binding resins with digoxin was reported, however, to have no effect on steady state serum glycoside levels (1). The area of the interaction of other drugs with the gastrointestinal absorption of digoxin has been little explored to date and is clearly a promising one for future investigation.

Summary

Digoxin tablets are incompletely absorbed by human subjects. Substantial differences in the bioavailability of currently marketed digoxin products have been demonstrated repeatedly. Differing pharmacokinetic patterns have been observed with various prep-

arations. The variation in absorption is not due to lack of tablet content uniformity. Therapeutic ineffectiveness has been noted with products of inferior bioavailability. Establishment of bioavailability standards, and governmental regulation of the problem, are urgently needed. A digoxin preparation that was 100% absorbed would not necessarily be ideal. Urinary digoxin excretion 24-hr after a single dose may prove to be a useful screening test for bioavailability. The cause of variation in the absorption of digoxin tablets remains to be established, but differences in the rate at which such tablets dissolve may be important.

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