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Editorial

Appraisal of digoxin bioavailability and pharmacokinetics in relation to cardiac therapy

John G. Wagner, Ph.D.
Ann Arbor, Mich.

Butler and Chen[1] first reported on the preparation of digoxin-specific antibodies. Later, Smith and associates[2,3] characterized the antibodies[2] and developed a radioimmunoassay for digoxin in serum or plasma.[3] Subsequently, it was shown that antibodies present in commercially available antiserum were not specific for digoxin, but that digoxin, digoxigen-mono-digotoxoside, and digoxigen-bis-digitoxoside all reacted with the antibody to about the same degree.[4,5] Digoxigenin also cross-reacted, but to a much lesser degree.[4,5] However, earlier studies[6,7] indicated that all the metabolites of both digoxin and digitoxin are cardioactive to varying degrees in both the guinea pig and the cat. Only the aglycones appear to have greatly reduced activity in vivo. Thus, what low levels of metabolites one would measure by application of the radioimmunoassay would mostly be cardioactive. Hence, from a clinical point of view, the radioimmunoassay procedure for digoxin is quite useful for monitoring individual patients, determining therapeutic and toxic plasma or serum levels, and in bioavailability studies where plasma or serum levels of digoxin and/or urinary excretion of digoxin are compared following administration of digoxin by different routes of administration (intravenously, intramuscularly, or orally) or as different commercially available dosage forms and specially made test formulations given by the oral route. The specificity of the digoxin radioimmunoassay has been improved by a consideration of reaction rates as well as avidities of various species to bind to the antibody.[8] Also, various modifications of the radioimmunoassay procedure have been published.[5,9,10]

The label dose of digoxin which appears on the container of the dosage form which is administered to the patient is not the same as the amount of digoxin which reaches the circulation, except when the drug is administered intravenously. When digoxin is administered orally or intramuscularly an amount less than the label dose reaches the circulation. The ratio of the amount which reaches the circulation to the label dose varies both with the route of administration and the particular commercially available dosage form which is administered. This bioavailability problem has been extensively studied recently.[11-25] The bioavailability of digoxin has been assessed by two different methods: (1) by comparison of the areas under the serum or plasma concentration curves in man (hereafter called the *area method*) and (2) by comparison of the relative amounts of digoxin excreted in the urine of man (hereafter called *urine method*). It is tenous to make interstudy comparison of results

From the Upjohn Center for Clinical Pharmacology, The University of Michigan, Ann Arbor, Mich.

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Reprint requests to: Dr. John G. Wagner, Upjohn Center for Clinical Pharmacology, The University of Michigan, Ann Arbor, Mich. 48104.

since investigators have used a wide variety of study conditions, such as the duration of the fasting period before and after the dose of digoxin; also they have varied the time interval of blood sampling and/or urine collection. In addition, some investigators have utilized normal human subjects and others have utilized cardiac patients. In most studies single oral doses have been administered to normal human subjects and biological specimens have been assayed by the radioimmunoassay method. In some studies multiple doses have been administered. Some authors have compared peak plasma or serum concentrations of digoxin. However, with digoxin, although such comparisons may have clinical significance, the ratios of average peaks really do not reflect bioavailability of digoxin. The more slowly absorbed preparations, such as tablets, yield peak levels much lower than those obtained by the intravenous route and with rapidly absorbed preparations, such as the elixir or aqueous solutions; and the ratio of average peak for a tablet/average peak following intravenous will usually be lower than the corresponding ratio by the area method or urine method. A consensus of the literature indicates that, based on the area and/or urine methods, the relative order of bioavailability of digoxin is as follows: Rapid intravenous injection or infusion > sterile aqueous solution administered intramuscularly ≥ elixir or aqueous solution administered orally > Lanoxin tablets* administered orally > various other brands and *chemically equivalent* tablets available to date from other manufacturers. Because of problems in interstudy comparisons it is difficult, if not impossible at present, to assign a numerical value for bioavailability for each of the above. However, some intrastudy results will be cited. It should be noted that the reference in each study is assigned a value of 1.0, but the reference varies from study to study—being sometimes intravenous infusion, sometimes the elixir administered orally, and sometimes Lanoxin tablets administered orally.

Based on calculation of 0 to 5 hour areas by the author from the data of Lindenbaum and associates,[12] tablets tested (and relative bioavailabilities) were as follows: Lot A_1 (1.0), Lot B_1 (0.71), Lot B_2 (0.14), Lot C (0.28). Lot A_1 was Lanoxin, Lots B_1 and B_2 were manufactured by American Pharmaceutical Company, and Lot C was manufactured by Davies Edwards.

Only tablets of Lot B_2 in the Lindenbaum study failed to meet the U.S.P. requirements for tablet-to-tablet variation in potency.[26,27] The comments of Wagner and colleagues[22] pertaining to the article of Feldmann[28] were in relation to Lots A_1 and B_2, both of which passed U.S.P. specification. Thus the subsequent comments of Feldmann[29] seemed unnecessary.

Based on calculation of 0 to 5 hour areas by the author from the data of Vieweg and Sode,[21] preparations tested at a 0.5 mg. dose level and relative bioavailabilities were as follows: Lanoxin pediatric elixir 0.05 mg. per cubic centimeter (Lot 592B) (1.0), Lanoxin tablets, 0.125 mg. (Lot 880A) (0.81), individually wrapped Lanoxin tablets (Lot 048A) (0.78), and Lanoxin tablets, 0.25 mg. (Lot 377A) (0.64). Analysis of variance of the areas indicated that the bioavailability of the elixir was significantly greater than that of the tablets, but that the bioavailabilities of the three lots of tablets did not differ significantly. This was only a four-subject study. The bioavailability of different strengths of Lanoxin tablets should be checked in a larger panel of subjects.

Based on calculation of 0 to 96 hour areas Wagner and associates[22] reported average relative bioavailabilities in two normal subjects, following 0.5 mg. single doses, as follows: intravenous infusion (1.0), solution of digoxin in 5 per cent dextrose orally (0.80), Lanoxin tablets, 0.25 mg. (Lot 999A) (0.57), and digoxin tablets, 0.25 mg. (Fougera & Co., Inc. Lot No. 1510) (0.31). In a separate crossover study in eight normal subjects the Fougera tablets yielded average peak plasma levels and 0 to 96 hour areas under the plasma level curves which were only 59 and 55 per cent, respectively, of those attained with the Lanoxin tablets.

Greenblatt and colleagues[25] administered single doses of 0.75 mg. of digoxin. Based on 0 to 8 hour areas and six-day urinary excretion their data indicate the following relative bioavailabilities: intravenous infusion (1.0), Lanoxin injection, intramuscularly (0.80 and 0.83), Lanoxin pediatric elixir, 0.05 mg. per cubic centimeter orally (0.67 and 0.65), Lanoxin tablets, 0.25 mg. orally (Lot 915E) (0.44 and 0.55). These authors[25] also reported highly significant correlations between six-day urinary excretion of digoxin and

*Lanoxin tablets are manufactured by Burroughs-Wellcome & Co., U. S. A.

area 0 to 8 hour under the serum concentration curve, and between six-day urinary excretion and first-day urinary excretion of digoxin.

The above examples pertain to digoxin preparations available in the United States. The bioavailability literature on digoxin is complicated since the Lanoxin tablets available in the United Kingdom are not the same as those available in the United States. In May, 1972, Burroughs Wellcome & Co. in the United Kingdom altered the production process for their Lanoxin tablets. The absorption of the new English Lanoxin tablets was presented by the manufacturer as being about twice that of tablets produced before May, 1972. This value of double the amount absorbed was supported by other investigators.[15,20] However, it appears that the bioavailability of the new United Kingdom Lanoxin tablets is very similar to that of the Lanoxin tablets which have been available in the United States to date.

The rate of dissolution of digoxin from various commercial tablets in vitro has been correlated with bioavailability of digoxin in man as assessed by the area and urine methods.[22-24] Since May, 1972, all batches of Lanoxin tablets made in the United Kingdom have been subjected to a dissolution test to ensure consistently high dissolution rate.[23] Extensive studies have also been carried out in the United States. In the future it may be possible to exclude poorly performing digoxin tablets from the American market by establishing in vitro rate of dissolution specifications.

When digoxin has been administered orally in the form of a hydroalcoholic solution (elixir) or in aqueous solution most investigators[21,22,24] have reported lower plasma or serum levels and per cent of dose excreted in the urine (hence lower bioavailabilities by the area and urine methods) than the known 100 per cent bioavailability attained by the intravenous route. Some possible reasons for this are as follows: (1) Part of the administered dose of digoxin is metabolized and the major part (about 80 per cent) is excreted unchanged in the urine.[30] When digoxin is administered orally all of the drug ultimately absorbed passes via the portal vein to the liver, where it is available to metabolizing enzymes. When the drug is administered intravenously only a portion of the blood reaches the liver on each circulation pass. This so-called "first-pass effect"[31] following oral administration can account for some, but not all, of the reduced bioavailability of digoxin when it is presented in solution orally. (2) There may be a "window effect" such that digoxin is only absorbed very rapidly from solution in the upper part of the gastrointestinal tract. Hence part of the solution of digoxin, after mixing with gastrointestinal contents, passes the "window," due to gastrointestinal motility, before it can be all absorbed. (3) Intestinal tissue in the guinea pig, and possibly in man, can metabolically degrade digitalis glycosides.[32] (4) Digoxin may have an unfavorable in vivo partition coefficient between the membrane and gastrointestinal fluids.[33] (5) Acidic gastric juice (below pH 3) is capable of hydrolyzing digoxin.[34]

Why do solid oral dosage forms, such as tablets, allow less digoxin to be absorbed than when the digoxin is administered orally as a solution? Most investigators have attributed this to the slow rate of dissolution of digoxin from tablets.[14,17,20,23] Owing to the "window effect" normal gastrointestinal travel rates are such that there is not enough time for all the digoxin to reach the solution state and become absorbed. However, this does not explain the results with all commercially available tablets. With some tablets their construction and ingredients are such that some of the digoxin is "locked up" in the small particles produced after the tablet disintegrates. Some digoxin apparently passes through the gastrointestinal tract in the solid state and never reaches the solution state. Evidence for this phenomenon is that when such tablets are subjected to in vitro rate of dissolution tests only part of the label dose of digoxin is ultimately released even after the dissolution tests are run for long periods of time. An example is digoxin tablets of Lot B_2 in Lindenbaum and associates'[12] study which gave very low plasma levels of digoxin. When this lot was tested in vitro by Wagner and colleagues[22] it released in vitro an average of only 1.2 per cent of its digoxin content when stirred at 50 r.p.m. in 500 ml. of water at 37° C. for two hours. When the stirring rate was increased to 200 r.p.m. for an additional hour, the tablets had released a total of only 3.6 per cent of their digoxin content. By the normal official tablet assay procedure the digoxin content of these tablets could be determined. Hence the problem with this marketed Lot B_2 of Lindenbaum and associates[12] was not only that it was out of compliance with United States Phar-

macopoeia specifications for tablet-to-tablet variation in potency[26] but also the tablet exhibited extremely poor dissolution characteristics.[22] Only a small amount of the labeled dose was released in the in vitro dissolution test and a similar situation presumably existed in the gastrointestinal tract of man. The particle size of the digoxin used in the preparation of digoxin tablets may also be a determinant of the bioavailability of digoxin. Reduction of the particle size of digoxin used to prepare experimental tablets and capsules was shown to cause an increase in serum digoxin concentrations compared with results achieved with coarse digoxin particles which met the requirements of the British Pharmacopoeia.[19] Such factors as the type and amount of disintegrating agent, diluent, and other excipients in the tablet with digoxin, and the compressional force used to prepare the tablets, can alter bioavailability of digoxin.

Digoxin is 25 per cent bound to serum proteins and the remainder is free in solution in serum. The portion protein bound is entirely bound to human serum albumin (HSA). The binding capacity of HSA is greatly in excess of therapeutic concentrations. Under equilibrium conditions digoxin is reversibly bound to the red cell membrane and a simple washing procedure is sufficient to displace digoxin from the erythrocytes.[35]

The elimination half-life of digoxin in cardiac patients and subjects with normal renal function averages 1.5 to 1.7 days.[18,36] Similar values are obtained from studies with tritiated digoxin[36] as those in which cold digoxin was administered and samples were assayed by the radioimmunoassay procedure.[18] Such half-lives were determined from terminal plasma concentration data—i.e., enough time was allowed after dosing so that absorption was complete (if the drug was given orally) and distribution equilibrium had been attained (if the drug was given intravenously or orally). Following massive doses of digoxin shorter half-lives of digoxin (10 to 20 hours) have been reported[37-40] but the data presented indicate that these "half-lives" were estimated from plasma digoxin levels during the absorption-distribution phase and are not comparable to the half-lives as usually estimated. Half-lives estimated from plasma concentrations during the absorption-distribution phase will always be less than the half-life estimated from terminal plasma concentrations. Thus there is no real evidence to date of any difference in the true elimination half-life of digoxin following massive doses compared with therapeutic doses. All one can really say from data published to date is that after massive doses of digoxin both the absorption and distribution phases are much longer than following therapeutic doses. This explains some of the questions raised in a recent editorial.[41]

Bloom and Nelp[42] showed that, within error, the renal clearance of tritiated digoxin is equal to the renal clearance of creatinine, and that the plasma half-life of digoxin increased with decrease in the creatinine clearance. Doherty and associates[43] reported serum digoxin half-lives averaging 3.9 days (range 2.5 to 5.5 days) in eleven anephric patients. They stated that in their experience anephric patients may be maintained on one half to two thirds of the usual dose of digoxin. For patients with impaired renal function it has been shown that the elimination rate constant of digoxin, K% (daily loss as per cent per day), is a linear function of endogenous creatinine clearance.[44] The data of Jelliffe[45] gave the equation:

$$K\% = 16.4 + 0.259\,Cl_{cr}$$

where Cl_{cr} is the endogenous creatinine clearance in milliliters per minute per 1.73 square meters of body surface area. The data of Bloom and Nelp[42] gave the equation:

$$K\% = 20.0 + 0.173\,Cl_{cr}.$$

The K% for patients with normal renal function is given by substituting $Cl_{cr} = 100$ into these equations; performing this operation gives normal K% values of 42.3 and 37.3 per cent per day, respectively. The elimination half-life is then obtained by dividing the K% value into 69.3; the above normal K% values yield half-lives of 1.6 and 1.9 days, respectively. For a patient with impaired renal function one substitutes the patient's Cl_{cr} value into the equation and obtains a (K%) patient. The patient maintenance dose is then calculated by the formula:

$$\text{Patient maintenance dose} = \text{normal maintenance dose} \times \frac{(K\%)\ \text{patient}}{(K\%)\ \text{normal}}.$$

Recently Reuning and colleagues[46] have presented evidence that the volume of distribution

of digoxin is lower in patients with impaired renal function than in subjects with normal function. Steady state volumes of distribution (V_dSS) averaging 330 and 510 L. respectively, were reported. Thus, the steady state volume of distribution of patients with impaired renal function averages only 65 per cent of that of patients with normal renal function. On the basis of this and other evidence these authors recommended that the loading dose of digoxin for patients with severely impaired renal function be decreased to one half to two thirds of the normal loading dose in order to achieve blood levels of digoxin in the desired therapeutic range.

There are problems in applying simple linear pharmacokinetic models to digoxin. Some of these are as follows: (1) Plasma or serum digoxin concentrations plateau from about two to seven hours after cessation to an intravenous infusion[22] or following rapid intravenous injection of tritiated digoxin.[47] Such a plateau is disregarded in simple linear compartment analysis. (2) When radioactivity is measured following tritiated digoxin and when the radioimmunoassay procedure is used following cold digoxin, some metabolites of digoxin are measured as well as unchanged drug.[4,5] Pharmacokinetic modeling assumes measurement of only one species. (3) Bile cycling of digoxin exists in man[36] and can cause secondary peaks on plasma digoxin concentration curves when patients eat soon after an oral dose.[20] Even in the absence of such visible evidence bile cycling still exists yet application of the simple two-compartment open model ignores this. (4) There is evidence of nonlinear tissue binding of digoxin[48] whereas the simple linear models assume linear binding. Nonlinear binding would result in the ratio of tissue concentration/plasma concentration decreasing as the plasma concentration increases.

Chiefly because of flexibility of route of administration and intermediate duration of action, digoxin has become the digitalis glycoside predominatly used in hospitalized patients and, to a somewhat lesser extent, in office practice.[49] Recent studies suggest that digoxin *per se* is still an excellent drug, but that one must be much more careful in its use since new factors have come to the light. *The Medical Letter*[50] recently published guidelines on the choice of a digoxin product and the author agrees with the statements therein. Some quotations are:"... digoxin tablets of poor bioavailability continue to be marketed and the practicing physician must be aware that underdigitalization or toxicity may result from changes in source of lot of digoxin. Switching back and forth between digoxin tablets from different manufacturers should not be encouraged at this time. If the physician has any reason to question the effectiveness of a digoxin preparation, serum digoxin concentrations should be measured in blood taken eight hours or more after the last oral dose (usual therapeutic serum range, 0.5 to 2.0 ng. per milliliter)... many cardiologists advise that only Burroughs-Wellcome digoxin (marketed in the United States as Lanoxin) should be used while awaiting industry-wide establishment of dissolution rate standards by the FDA."

When digitalizing patients by the intravenous route it must be remembered bioavailability of digoxin by this route is from 1.6 to 2 times that attained with Lanoxin tablets. Also, no longer should doses given as Lanoxin pediatric elixir be exactly equated with doses given as Lanoxin tablets since the elixir provides higher peaks and areas for the same dose than the tablets.

The author disagrees with Reuning and associates[46] that the loading dose of digoxin should be reduced in patients with severe renal failure and will publish the reason in the near future.

Compliance is also a determinant of serum digoxin concentration.[51] Formulas for establishing optimum digitalization based on age, renal function, and other factors do not apply to patients who do not take their medications. Compliance cannot be ignored as a determinant of therapeutic response to digoxin. Patients must be adequately counselled as to the importance of taking their medicine.

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