Relationship Between Plasma Concentration and Dose of Digoxin in Patients With and Without Renal Impairment

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SUMMARY: The purpose of this study was to determine if there is a linear relationship between oral doses of digoxin and various measurements of steady-state digoxin plasma concentration and urinary excretion in patients with a wide range of renal function. Ten patients (mean age 58 years) with creatinine clearances > 50 ml/min/1.73 m² BSA (mean creatinine clearance 80 ml/min/1.73 m² BSA) and nine patients (mean age 61 years) with creatinine clearances < 50 ml/min/1.73 m² BSA (mean creatinine clearance 20 ml/min/1.73 m² BSA) were given digoxin tablets orally at two or three different dose levels (dose range 0.0313–0.5 mg/day). After a dosing period equal to at least five half-lives, three to four consecutive daily digoxin plasma concentrations were determined. Plasma concentrations and urinary digoxin excretion were measured during one 24-hour dosing interval at each dose level. Digoxin plasma and urine concentrations were determined in triplicate using radioimmunoassay. Individual patient plots provided evidence of linearity for digoxin 24-hour steady-state plasma concentration vs dose; digoxin 24-hour cumulative urinary excretion vs dose; and area under the digoxin plasma concentration-time curve during a 24-hour dosing interval vs dose. Absolute values for these various parameters indicated substantial interpatient variation probably due to patient differences in both digoxin absorption and digoxin total body clearance.

These results indicate that there is a linear relationship between digoxin plasma concentration and dose in patients with normal and decreased renal function. This linearity is support for dose-independent pharmacokinetics of digoxin in man. We conclude from these data that a change in digoxin dose should result in a proportional change in digoxin plasma concentration over the dose range examined.

THERE APPEARS TO BE a dose-response relationship for digoxin. Further, it is desirable to obtain the maximal total body dose consistent with minimal risk of digitalis toxicity. Finally, it is generally agreed that the incidence of digitalis toxicity increases substantially when the serum digoxin level is above 2 ng/ml in adults. These observations have led to an attempt to regulate serum digoxin levels to a range somewhat greater than 1 ng/ml, but less than 2 ng/ml for most patients, with the realization that occasionally a patient may become toxic at these levels and some patients may require a level in excess of 2 ng/ml to adequately control ventricular response to atrial fibrillation or to achieve a needed inotropic response. A frequent problem arises when a digoxin level is found to be low on an initial dose of digoxin, since the exact increment in digoxin dose that is required to raise the digoxin level to a desired value is unknown. Theoretically, there should be a linear relationship between increase in oral dose and increase in serum levels in the same patient if the following are constant: rate and extent of absorption, serum half-life, volume of distribution, and dosing interval. It was the purpose of this study to define the relationship between serum concentration and dose of digoxin in patients with normal renal function and in patients with varying degrees of renal function impairment. This relationship is of clinical importance, since this information is needed in order to predict plasma digoxin concentrations in response to changing digoxin doses.

Methods

The study population included 10 patients taking digoxin for either mild congestive heart failure or atrial fibrillation who had creatinine clearances > 50 ml/min/1.73 m² BSA (group 1) (mean age 58 years) and nine patients with creatinine clearances < 50 ml/min/1.73 m² BSA (group 2) (mean age 61 years). The separation of patients into two groups based on arbitrary creatinine clearance values was solely for the purpose of assigning patients to one of two protocols designed to avoid digoxin toxicity, since the final data analysis examined the entire spectrum of renal function. Clinical data on the study patients are listed in table 1. Patients on a hemodialysis program, patients with severe congestive heart failure as defined by elevated jugular venous pulsations, diffuse pulmonary rales, an S₃ gallop, and patients taking quinidine,
cholestyramine, kaolin-pectin, neomycin, or antacids were excluded from the study. All patients had stable creatinine clearance values for at least three months before the start of the study. Patients were selected in both groups who had normal values for the following tests: 1) liver function tests (serum glutamic oxaloacetic transaminase, alkaline phosphatase, total and direct bilirubin, and serum glutamic pyruvic transaminase); 2) thyroid function tests (T₃, T₄); and 3) serum potassium. In addition, all patients had the following obtained at the beginning of the study and before each new dosing period: 1) interview and physical examination; 2) ECG with rhythm strip after 5 minutes of rest and every 5 minutes during 30 minutes; 3) creatinine clearance and serum creatinine; and 4) serum albumin. Creatinine concentration was determined using a modification of the Technicon autoanalyzer adaption of the technique of Folin and Wu, which increased the precision of the plasma creatinine determination by expanding by threefold the 0–1 mg/100 ml reading range.¹ The within-day precision (coefficient of variation) for a 10 mg/dl control plasma solution was 2.07% (n = 10). The accuracy was ± 0.015 mg/dl. The within-day precision (coefficient of variation) for a 10 mg/dl control plasma solution was 1.38% (n = 12). The accuracy was ± 0.034 mg/dl. Informed consent and a chest radiograph were obtained at the beginning of the study.

Lanoxin brand digoxin (Burroughs Wellcome and Company) from a single lot number (#330-W) was used. In vitro dissolution tests performed by Burroughs Wellcome and Company on the study lot indicated that 85.5% of the dose dissolved within 1 hour. Tablets were supplied as 0.0625 mg, 0.125 mg, and 0.25 mg tablets. Tablet counts were made to assure patient compliance. Blood samples were drawn from a forearm vein 24 hours after the preceding dose. A sample was obtained on each of three to four consecutive days at each steady-state level. Half of the plasma from each sample was used for measurement of a digoxin plasma concentration for further dose adjustment, while the other half was frozen for simultaneous analysis after the various doses had been given. Digoxin concentration was measured in plasma and urine samples by radioimmunoassay as previously described.² In the urine assay, 0.1 ml of concentrated digoxin standard solution or 0.1 ml of urine was

<table>
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<th>Table 1</th>
<th>Clinical Data on Study Patients</th>
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Abbreviations: Wt = weight (ideal weight determined from ref 4); BSA = body surface area; K⁺ = serum potassium concentration.
diluted with 2 ml of phosphate-buffered saline. One-half-milliliter aliquots of each of these solutions were assayed. All assays were performed in triplicate, and the external standard channel ratio method was used for quench correction. All plasma and urine concentrations for each patient were determined at the same time using the appropriate standard curve. The assay precision was determined by at least 20 measurements each of three plasma pools of varying digoxin concentrations. The coefficients of variation were: 9.1% at a plasma digoxin concentration of 0.55 ± 0.05 ng/ml, 4.6% at a mean of 1.31 ± 0.06 ng/ml, and 4.3% at a mean of 2.66 ± 0.11 ng/ml. The between-day precision measured on 12 different days was 3.4% with a mean of 1.57 ± 0.05 ng/ml. The average minimal detectable plasma concentration was 0.07 ng/ml. The coefficient of variation for the digoxin urine assay was 3%, with a mean concentration of 46.5 ± 1.4 ng/ml. The patients were hospitalized to obtain a 24-hour urine collection and plasma samples were obtained at 0, ½, 1, 2, 4, 6, 8, 12, and 24 hours during each dosing interval at each steady-state. Blood samples were obtained from the arm using a small plastic catheter sealed on the distal end and flushed with heparin after each blood sample was withdrawn to prevent clotting. Patients in group 1 had plasma concentrations measured after being given an equivalent maintenance dose of Lanoxin brand digoxin from the study lot for 10 days. Subsequent doses were determined according to the initial steady-state plasma level as follows:

The digoxin level on the initial maintenance dose is shown in column 1. The subsequent digoxin doses are shown in columns 2 and 3.

1
A) Initial level between 0.6–0.7 ng/ml
B) Initial level between 0.8–0.9 ng/ml
C) Initial level between 1.0–1.4 ng/ml
D) Initial level ≥1.5 ng/ml

2
† dose by 50%
‡ dose by 50%
§ dose by 75%

3
† dose by 100%
‡ dose by 100%
§ dose by 50%

(only if initial dose is ≥ 0.25 mg qd)

Patients took the prescribed dose at each dosing interval for at least 10 days before digoxin level determinations. Patient compliance was determined by: 1) providing separate packages of tablets for each dosing interval; 2) tablet counts; and 3) patient interviews at each steady-state.

Patients in group 2 had the digoxin half-life determined by measuring digoxin plasma concentrations in blood samples taken at 24, 48, 72 and 96 hours after an initial oral dose of 0.5 mg of digoxin. These patients were then started on a daily dose of 0.125 mg qd. This initial dose of digoxin, 0.125 mg each day, was selected for patients with renal failure based on the studies of Doherty and associates. Subsequent doses were determined according to the digoxin level on the initial dose of 0.125 mg qd, as shown in column 1. These doses are shown in columns 2 and 3.

2
A) Initial level between 0.5–0.6 ng/ml
B) Initial level between 0.7–0.9 ng/ml
C) Initial level between 1.0–1.4 ng/ml
D) Initial level ≥1.5 ng/ml

3
0.25 mg qd
0.0625 mg qd
0.0625 mg qd
0.0625 mg qd
0.375 mg qd
0.25 mg qd
0.1875 mg qd
0.0625 mg qd

Patients took the prescribed dose at each dosing level for a period of time equal to at least five half-lives before digoxin level determinations. The same protocol for collection of blood and urine detailed above for patients in group 1 was followed for patients in group 2.

The study was terminated if a digoxin level of 2 ng/ml or greater was associated with: 1) symptoms of nausea, vomiting, diarrhea, depression, confusion, delirium, neuralgias, alterations in color vision, scotomas, blurring, or shimmering, or 2) electrocardiographic evidence of arrhythmias that could have been interpreted as evidence of toxicity, such as an increase in premature ventricular contractions, ventricular tachycardia, atrial tachycardia with block, Wenckebach phenomena, complete AV block or complex arrhythmias.

Renal clearance of digoxin was calculated according to the formula

\[ \text{Cl}_{\text{dig}} = \frac{X_u}{\text{AUC}} \]

where \( X_u \) is the 24-hour urinary digoxin excretion during a dosing interval at steady-state and AUC is area under the plasma concentration vs time curve (using the trapezoidal rule) during a dosing interval at steady-state.

Three patients with severe renal failure in group 2 who received a digoxin dose every 48 hours had steady-state plasma concentrations determined at 48 hours just before the next dose. In these patients, the plasma concentration vs time curve after a single dose of digoxin at steady-state was constructed over 48 hours and one-half of the value for the area under the curve was recorded as the AUC.

Results

Group 1 consisted of 10 patients with creatinine clearances between 56–110 ml/min/1.73 m² BSA (mean creatinine clearance 80 ml/min/1.73 m² BSA). Group 2 consisted of nine patients with creatinine clearances between 7–38 ml/min/1.73 m² BSA (mean creatinine clearance 20 ml/min/1.73 m² BSA). Values for creatinine clearance at the beginning and at the end of the study were not significantly different from values obtained at least three months before the study. The study was terminated in the 20th patient after the...
patient presented with rapidly deteriorating renal function requiring hemodialysis. It was not necessary to terminate any patient study because of non-compliance or digoxin toxicity. None of the patients had a significant change in serum albumin level during the study.

A plot of the steady-state 24-hour plasma digoxin concentration vs digoxin dose (corrected for body weight) is presented in figure 1 for patients from group 1 and group 2. Normalization for body weight used either actual body weight or ideal body weight, whichever was the smaller value, since digoxin concentration is extremely low in adipose tissue. The lines for each patient in both groups show a linear relationship between steady-state plasma digoxin concentration and digoxin dose. The data show steeper slopes for the patients in group 2 with severe renal failure compared with the group 1 patients with normal or mildly impaired renal function. However, within each group there is not a consistent relationship between the steepness of the slope and the creatinine clearance.

The results of the study for patients in groups 1 and 2 are presented in table 2. Steady-state 24-hour plasma digoxin concentration (C) has been normalized for dose of digoxin (X°) and for body weight (wt) (i.e., normalized C = C/X°/wt). The same normalization procedure has been used for steady-state area under the plasma concentration vs time curve (AUC; normalized AUC = AUC/X°/wt).

Plots similar to figure 1 relating 24-hour urinary digoxin excretion to dose, and area under the curve to dose demonstrated a linear relationship between X° and body weight (wt) and between AUC and X°.

Figure 2 presents the relationship between the mean ratio of digoxin steady-state plasma concentration to digoxin dose (C/X°) and the mean creatinine clearance corrected for body surface area (Clcr ml/min/1.73 m² BSA) for each patient. These data have been fitted by nonlinear regression analysis, using a computer program, to an equation which has the form, \[ y = \frac{1}{ax + b}, \] where “a” and “b” are constants, “x” represents creatinine clearance, and “y” represents the ratio of C/X°. The solid curve in figure 2 represents the line which best fits these data. Estimates of the constants “a” and “b” may be obtained from a plot of X°/C vs creatinine clearance. A plot of the latter two parameters gives a straight line relationship.

Figure 1. Steady-state 24-hour plasma digoxin concentration (ng/ml) plotted against daily digoxin dose corrected for body weight (mg/day/kg body weight). Solid lines indicate patients from group 1 with creatinine clearances > 50 ml/min/1.73 m² body surface area (BSA). Dashed lines indicate patients from group 2 with creatinine clearances < 50 ml/min/1.73 m² BSA.
<table>
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<th>Patient no.</th>
<th>Dose X°C</th>
<th>C (ng/ml) mean ± sd</th>
<th>C/X°/Wt (×10⁴) (ml/kg)</th>
<th>Xµ (µg/24 hr)</th>
<th>AUC/X°/Wt (×10⁴) (hr/ml/kg)</th>
<th>Cldig (ml/min/1.73 m² BSA) mean ± sd</th>
<th>Cler (ml/min/1.73 m² BSA) mean ± sd</th>
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*Incomplete urine collection.

Abbreviations: X°C = daily digoxin dose; C = steady-state 24-hour plasma digoxin concentration (mean of three or four determinations); Xµ = 24-hour urinary digoxin excretion after a single dose at steady-state; AUC = area under plasma concentration vs time curve after a single dose at steady-state; Cldig = renal clearance of digoxin normalized for 1.73 square meters of body surface area (mean of three values at each dose); Cler = creatinine clearance normalized for 1.73 square meters of body surface area (mean of three values at each dose); TTP = time to peak digoxin plasma concentration after oral dose; ND = not done.
Figure 2. Steady-state 24-hour plasma digoxin concentration (C) normalized for digoxin dose (X) vs creatinine clearance (Clcr) corrected for 1.73 m² body surface area. The solid line represents the nonlinear regression fit of the data. The equation of the best fit line for these data is as follows:

\[ y = \frac{1}{(ax + b)} \]

where \( a = 4.18 \times 10^3 \) min/1.73 m²; \( b = 4.8 \times 10^4 \) ml; \( x = \text{creatinine clearance in ml/min/1.73 m²} \).

Figure 3 presents the relationship between Clcr (ml/min/1.73 m² BSA) and the renal digoxin clearance Cldig (ml/min/1.73 m² BSA). The formula for the regression equation is \( y = (0.99)X + 7.36 \) with a correlation coefficient of \( r = 0.93 \). The correlation between the percent of a digoxin dose excreted in 24 hours and creatinine clearance is not as good, \( r = 0.75 \). The square of the correlation coefficient is 0.56. This means that 44% of the variation in urinary digoxin excretion is not accounted for by creatinine clearance. This poorer correlation can be partly explained by interpatient variability in digoxin absorption and metabolism patterns. This demonstrates the limitation of creatinine clearance in predicting the excretion of digoxin.

Discussion

There have been conflicting reports regarding the linear or nonlinear relationship between digoxin levels and dose. Redfors et al. found a linear relationship between dose and serum drug levels of digoxin in i-
individual patients with normal renal function. Brown and Abraham\textsuperscript{a} and Hoeschen et al.\textsuperscript{b} demonstrated a linear relationship between oral digoxin dose and mean serum levels for a group of patients. Dobbs et al.\textsuperscript{c} demonstrated a linear relationship between oral loading dose of digoxin and serum concentrations 24 hours after the dose. However, Huffman et al.\textsuperscript{d} reported a nonlinear relationship between oral digoxin dose and serum levels for patients with normal renal function. The relationship between the area under the serum concentration-time curve and oral dose was also nonlinear. Morrison et al.\textsuperscript{e} also reported a nonlinear relationship between oral digoxin dose and mean serum levels for a group of patients. The linear or nonlinear relationship between digoxin levels and dose has not previously been systematically investigated in patients with stable chronic renal failure.\textsuperscript{f}

Studies by Gierke et al.\textsuperscript{g} from our laboratory demonstrated a decreased volume of distribution for digoxin in azotemic dogs. Patients with severe renal functional impairment have also been reported to have a decreased volume of distribution for digoxin.\textsuperscript{h} Jusko and Weintraub's finding of altered tissue:serum concentration ratios in relation to renal function was consistent with this relatively smaller apparent volume of distribution of digoxin in patients with impaired renal function.\textsuperscript{i} Prior to the present study, it was not known whether this decreased volume of distribution in patients with renal failure was dose-dependent. Our study demonstrates a linear relationship between dose and plasma concentration for patients with normal renal function as well as in patients with abnormal renal function. The steeper slope of the steady-state digoxin concentration vs dose line for patients in group 2 compared to patients in group 1 (fig. 1) is consistent with a decreased total body clearance for digoxin in these patients with renal failure. This decreased clearance in chronic renal failure appears to have no effect on the linear relationship between digoxin concentration and dose.

Our finding of a linear relationship between dose of digoxin and steady-state concentration is in agreement with the findings of Hoeschen et al.\textsuperscript{a} These authors noted that increasing serum digoxin levels within the therapeutic range correlated with increasing improvement of left ventricular function as assessed by systolic time intervals. Redfors\textsuperscript{j} demonstrated that the ventricular response to atrial fibrillation is progressively decreased with increasing digoxin doses in the individual patient. Therefore, it is desirable and may be important in the individual patient to maximize the serum digoxin level without reaching a toxic level. Smith et al.\textsuperscript{k} have defined toxic levels by showing that all of their patients who were clinically toxic with digoxin had serum concentrations greater than 2 ng/ml. Ninety-five percent of their patients who were not toxic clinically had digoxin serum concentrations less than 2 ng/ml. Subsequently, this data of Smith's have been verified by many investigators, but it is widely recognized that there is overlap and patients may be toxic with levels of less than 2 ng/ml and other adult patients can tolerate serum concentrations well above this level.

A frequent problem arises when a digoxin level is found to be low while the patient is receiving a daily maintenance dose of digoxin. Lack of compliance is probably the most common cause of unexpectedly low serum digoxin levels in ambulatory patients. However, if this is excluded as a cause for a low digoxin level, then the physician must decide on an appropriate increment in dose. The exact increment in digoxin dose that is required to raise the digoxin concentration to a level less than 2 ng/ml, but to a level high enough to maximize the therapeutic effect, has not been determined. It has been proposed that digoxin distribution and elimination in man is described by a linear two-compartment open kinetic model.\textsuperscript{l} Therefore, there should be a linear relationship between increase in oral dose and increase in serum levels in the same patient if the following are constant: rate and extent of absorption, serum half-life, volume of distribution and dosing interval.

The results of our study are in agreement with the theoretical prediction of a linear relationship between increase in oral dose and increase in plasma concentrations of digoxin in the same patient (fig. 1). The linear model is further supported by the linear relationship between AUC and oral dose and between 24-hour urinary digoxin and oral dose. Renal clearance of digoxin did not change significantly with change in dose in the same patient.

The relationship between the steady-state plasma digoxin concentration normalized for dose (C/X\textsuperscript{m}) and creatinine clearance (fig. 2) demonstrates that one may have very little increase in the C/X\textsuperscript{m} ratio as the creatinine clearance decreases from normal to approximately 50 ml/min/1.73 m\textsuperscript{2} BSA. The C/X\textsuperscript{m} ratio rises rapidly as the creatinine clearance decreased below 15 ml/min/1.73 m\textsuperscript{2} BSA. Clinically, these data suggest that patients with mild to moderate reductions in creatinine clearances may need very little, if any, reduction in maintenance digoxin dose. In patients with severe renal failure, minor changes in creatinine clearance will cause major changes in the C/X\textsuperscript{m} ratio. Such dramatic changes may require very careful readjustment in digoxin dosing. There is also considerable interpatient variation. Thus, dosing of digoxin based primarily on serum creatinine or creatinine clearance must be employed with caution.

A linear relationship has been reported by Ewy et al.,\textsuperscript{1} Bloom and Nelp\textsuperscript{2} and Doherty et al.\textsuperscript{3} for creatinine clearance and renal digoxin clearance for clearances greater than about 40 ml/min. Our study demonstrates a linear relationship down to creatinine clearance values of 7 ml/min.

The time to the peak of the concentration-time curves was visually estimated and recorded in table 2. There is a trend toward a delay of peak concentration time with smaller doses. In nine of the 19 patients, the time of peak plasma concentration was later with smaller digoxin doses. These cases were equally
divided between the two groups. In eight patients, there was no change in the time to peak concentration. In two patients, 1 and 6, there was an inconsistent relationship between time to peak concentration and dose. The reason for this apparent shortening of the time to peak concentration after an oral dose with higher doses in some patients is unclear and requires further study.

We have demonstrated a linear relationship between the steady-state plasma digoxin concentration and increasing doses of digoxin for patients with varying degrees of renal function. This finding of a linear relationship can be clinically useful in predicting digoxin level response to changing digoxin dosage. A serum digoxin level of about 1.5 ng/ml should be associated with a therapeutic effect without appreciable incidence of toxicity in the adult. Therefore, if a patient has a plasma or serum concentration of digoxin of 0.75 ng/ml, the physician can recommend that the patient double the dose of digoxin to achieve the desired level. The optimal serum concentration will vary, depending on the clinical circumstance, and a level of 1.5 ng/ml is suggested only as a guide to therapy. However, in order to apply this dose concentration relationship properly and safely to a clinical situation, care must be taken to assure the accuracy of the initial digoxin level determination. Samples must be obtained from the patient at steady-state 24 hours after the previous dose. At least two determinations on successive days should be performed to assure reproducibility. Used in this fashion, changes in digoxin dosing based on the linear relationships demonstrated by this study should decrease the likelihood of digoxin toxicity.

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