A Method of Determining the Dose of Digoxin for Heart Failure in the Modern Era

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Background: The therapeutic range for digoxin in heart failure has recently changed to become lower and narrower, and the new range is associated with improved mortality. However, dosing methods have not been modified to reflect this change. In this study, we sought to develop a new method to determine the initial dose of digoxin in patients with heart failure.

Methods: Over a 6-month period, medical records were screened and reviewed for hospitalized adult patients who had a steady state digoxin concentration. A multiple linear regression was estimated relating digoxin concentration, digoxin dose, creatinine clearance, and ideal body weight to generate an equation relating the dose of digoxin with these variables and a specific target digoxin concentration of 0.7 ng/mL (0.9 nmol/L). This new method was then compared with 2 existing methods.

Results: Included in the study were 54 patients (mean [SD] age, 68 [15] years, with a mean (SD) creatinine clearance of 50 (25) mL/min (0.8 [0.4] mL/s) and mean (SD) ideal body weight of 62 (11) kg. Our proposed method and the Jusko and Koup method were more accurate than the Jelliffe method in predicting digoxin concentration. Root mean square errors were as follows: for the Jelliffe method (using ideal body weight), 0.810; for the Koup and Jusko method (with heart failure), 0.401; our proposed method, 0.375. The proposed method was then used to create a dosing nomogram.

Conclusions: Because the new therapeutic window of digoxin is associated with improved outcomes, more intensive dosage refinement should be considered. To this end, we offer new dosing recommendations and a nomogram for determining the initial dose of digoxin in patients with heart failure.

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Digoxin is recommended as adjunctive therapy to angiotensin antagonists, β blockers, and diuretics in select patients with symptomatic heart failure.1,2 Despite its long history as an agent to treat heart failure, only recently has its effectiveness been linked to neurohumoral modulation in addition to positive inotropy through inhibition of sodium-potassium adenosine triphosphate. These neurohumoral actions are evident at low digoxin concentrations; further decreases in norepinephrine concentrations are not observed as the concentration of digoxin increases, that is, from 0.7 to 1.2 ng/mL (0.9-1.5 nmol/L).3 Consistent with these observations are the post hoc findings4,5 from the Digitalis Investigation Group. In the analysis of both men and women receiving digoxin for systolic heart failure,4 those with digoxin concentrations of 0.5 to 0.8 ng/mL (0.6-1.0 nmol/L) had a 6.3% lower all-cause mortality and a 5.9% lower hospitalization rate compared with patients receiving placebo. Patients with serum concentrations greater than 1.2 ng/mL (1.5 nmol/L) had an 11.8% higher mortality and also higher rates of hospitalization and digoxin toxicity than those treated with placebo. The post hoc analysis of women in the Digitalis Investigation Group trial5 yielded similar findings. These results are consistent with other retrospective analyses of large multicenter clinical trials studying the effects of digoxin patients with left ventricular dysfunction.6 In all, despite the lack of controlled prospective trials, the most recently recommended therapeutic range for digoxin when used in symptomatic heart failure is now 0.5 to 0.9 ng/mL (0.6-1.2 nmol/L)3 or less than 1.0 ng/mL (<1.3 nmol/L).2 This range is narrower and lower than the older window of 0.8 to 2.0 ng/mL (1.0-2.6 nmol/L), which was originally defined on the basis of the risk of digoxin toxicity not effectiveness.7,8 Historically, 2 methods have been used to estimate the initial dose of...
Table 1. Estimated RMS Errors and Corresponding 95% CIs

<table>
<thead>
<tr>
<th>Source and Method</th>
<th>RMS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jelliffe9,10</td>
<td>0.810 (0.614-0.944)</td>
</tr>
<tr>
<td>Total body weight</td>
<td>0.758 (0.557-0.895)</td>
</tr>
<tr>
<td>Koup and Jusko</td>
<td>0.460 (0.298-0.563)</td>
</tr>
<tr>
<td>No heart failure</td>
<td>0.401 (0.272-0.484)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0.375 (0.223-0.480)</td>
</tr>
<tr>
<td>Proposed method</td>
<td>0.375 (0.223-0.480)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RMS, root mean square error.

PATIENT SELECTION

The laboratory records of hospitalized adult patients who had a digoxin concentration determined over a 6-month period were used to screen for suitable patients. This screening procedure yielded 117 potentially eligible patients. The medical records of these patients were then reviewed for the following entry criteria: patients had to be older than 18 years with a presumed steady state digoxin concentration (ie, a concentration determined in the postdistributive state [at least 6 hours after oral digoxin administration]) when receiving a stable dose of digoxin for a suitable time period to reach steady state. In those patients with normal renal function (estimated creatinine clearance, >90 mL/min [>1.5 mL/s]), the patient needed to be receiving the same dosage of digoxin for at least 1 week and for those with reduced renal function (estimated creatinine clearance, <90 mL/min [<1.5 mL/s]), the dose of digoxin needed to remain unchanged for at least 1 month. Patients were excluded from the analysis for the following reasons: (1) the presence of significant drug-drug interactions (eg, amiodarone, quinidine, verapamil, or macrolide antibiotics), (2) documentation in the patient’s record of a history of poor medication adherence, or (3) the presence of end-stage renal dysfunction requiring dialysis or of unstable renal function (ie, acute renal failure). Patient inclusion required the unanimity of 3 investigators. In patients with multiple digoxin concentrations, only a single digoxin level that best represented steady state conditions (ie, the last trough concentration determined during hospitalization) was used in the analysis. During the study period there were no institutional guidelines with regard to digoxin dosing or target digoxin concentrations in patients with heart failure, inasmuch the method of choosing a digoxin dose (and the resultant digoxin concentration) for an individual patient reflected the clinical judgment of the patient’s physician. Digoxin plasma concentrations were measured by a turbidimetric inhibition immunoassay method using digoxin-specific antibodies (Synchron LX; Beckman Coulter, Fullerton, Calif). The lower limit of detection for this assay is 0.2 ng/mL (0.3 nmol/L), and the within-run variation is ±0.1 ng/mL (±0.1 nmol/L). Spironolactone does not interfere with the determination of digoxin concentration by this method; patients receiving concurrent therapy with this agent were therefore not excluded from the analysis.

DETERMINATION OF THE DOsing ALGORITHM

The linear regression relating the patient’s digoxin concentration to the steady state maintenance dose of digoxin, the creatinine clearance (calculated from serum creatinine; see the next subsection), and the patient’s ideal body weight (IBW) (calculated according to height; see the next subsection) was estimated from the observed data. These variables were chosen because they have been historically demonstrated to be the primary variables in determining the concentration of digoxin in the plasma for a given dose. The estimated equation served the purpose of relating the dose of digoxin as a linear function of creatinine clearance and body weight for a specific digoxin target concentration (ie, 0.7 ng/mL [0.9 nmol/L]). To construct a dosing nomogram, the lines of constant digoxin maintenance dose as a function of creatinine clearance and IBW were then derived from the linear relationships among the dose of digoxin, estimated creatinine clearance, and IBW.

COMPARISON WITH OTHER METHODS

The dosing algorithm derived from the data set of steady state digoxin concentrations and patient characteristics was compared with 2 frequently recommended methods: that of Jelliffe and that of Koup and Jusko. For the Jelliffe method, the predicted, or expected, digoxin plasma concentration (Cp0) in nanograms per milliliter was defined for each patient by

\[
C_{p0} = -0.416 + (0.185 \times TBS),
\]

where

\[
TBS = \left[ \frac{Dose_{ss}}{[14 + (Cl_{cr}/5)]/100} \right] \times BW
\]

is the total body stores of digoxin, Dose_{ss} is the maintenance dose of digoxin at steady state, Cl_{cr} is the creatinine clearance estimated from serum creatinine by the method of Cockcroft and Gault, and BW is the patient’s body weight (both IBW estimated from height by the method of Devine and total body weight were used separately to estimate different values for expected digoxin concentrations).
For the Koup and Jusko method,
\[ C_{po} = \frac{F \times Dose \times 1000}{C_{ldig} \times \tau}, \]
where \( F \) is the bioavailability of digoxin tablets (0.75), \( \tau \) is the dosing interval (once daily as 1440 min/d);
\[ C_{ldig} = (1.303 \times C_L) + C_{lnr} \]
is the clearance of digoxin, and \( C_L \) is the nonrenal clearance of digoxin, equal to 41 mL/min (0.7 mL/s) in patients with heart failure and 20 mL/min (0.3 mL/s) in patients without heart failure.11 Both of these values for nonrenal clearance were used separately to estimate different values for expected digoxin concentration.

The comparisons between the expected \( (C_{pe})\) and observed \( (C_{po})\) digoxin concentrations were estimated in terms of the root mean square error (RMS)17 as follows:
\[ RMS = \sqrt{\frac{1}{n} \sum_{i=1}^{n} (C_{po} - C_{pe})^2}. \]

Invariant plots,18,19 relating the average, \( (C_{po} + C_{pe})/2, \) of observed and expected digoxin concentrations with their half-difference, \( (C_{po} - C_{pe})/2, \) were constructed to complement the observed and expected digoxin concentrations with their half-clearance, and the IBW was estimated from the present data.20

The estimation of the linear regression required a complete set of variables for each patient. In 3 patients, 1 variable (ie, height to estimate IBW was unavailable) could not be gleaned from the patient’s medical records, leaving a complete set of 51 observations. The estimated linear regression based on this set of 51 observations relating the patient’s observed steady state digoxin concentration to the maintenance dose of digoxin (dose), the creatinine clearance \( (C_L)\), and the IBW was

\[ C_{po} = 1.345 + (0.287 \times \text{Dose}) - (0.007 \times C_L) - (0.011 \times \text{IBW}). \]

The analysis of variance F-ratio statistic for the overall linear fit was 5.687 \((P = .002)\). The error variance estimate was \( s = 0.151 \). Given a digoxin target concentration of 0.7 ng/mL (0.9 nmol/L), the resulting dose determination is estimated by

\[ \text{Dose} = -2.247 + (0.0244 \times C_L) + (0.0383 \times \text{IBW}) \]

where the dose of digoxin is coded as 1=0.0625 mg/d (or 0.125 mg every other day), 2=0.125 mg/d, and 3=0.25 mg/d.

The estimated standard deviation for the predicted concentration at the mean values (dose=0.132 mg, IBW=61.76 kg, and clearance=50.7 mL/min [0.8 mL/s]) was 0.089. The estimated RMS errors and corresponding approximate large-sample 95% confidence intervals for the RMS estimates are shown in Table 1. The confidence intervals clearly indicate the superiority (in RMS terms) of the Koup and Jusko method and our proposed method relative to Jelliffe method. There is no statistical distinction between the method proposed here and the Koup and Jusko method based on these confidence intervals. Because the (square) bias is one of the components of the RMS – accuracy,17 we evaluated the paired mean differences \((C_{pe} - C_{po})\) of digoxin concentrations (Table 2).
Figure 1. Invariant plots relating observed and predicted serum digoxin concentrations. Each of the invariant plots shown here plots the mean digoxin plasma concentration between observed (Cpo) and expected (Cpe) on the x-axis and the difference between observed and expected (divided by 2) on the y-axis. Invariant plots using the Jelliffe dosing method are depicted in A (using ideal body weight) and B (using total body weight). Invariant plots using the Koup and Jusko (Koup et al and Jusko et al) dosing method are depicted in C (using nonrenal clearance values for digoxin in the absence of heart failure) and D (using nonrenal clearance values for digoxin in the presence of heart failure). E, The invariant plots using the proposed digoxin dosing nomogram described in the text and depicted in Figure 2. RMS denotes root mean square error.
Complementing the RMS analysis, the invariant plots for all 5 methods are shown in Figure 1. Note that these plots add the information of whether the differences between observed and predicted concentrations vary with the magnitude of the mean responses. The invariant plot for 2 coincident data points would reduce to a single point over the horizontal line at zero. Points clustering tightly around that line correspond to a smaller RMS. We observed that both the proposed method and the Koup and Jusko method are comparable in those 2 aspects and show deviations from zero that are more uniform (in the mean value axis) relative to the Jelliffe method.

In addition, all methods of dosing showed statistically significant (all P<.01) correlations between expected and observed digoxin concentrations: for the Jelliffe method using IBW (r=0.484), for the Jelliffe method using total body weight (r=0.379), for the Koup and Jusko method with heart failure (r=0.494), and for the Koup and Jusko method without heart failure (r=0.441). As could be expected, using IBW for the Jelliffe method and heart failure clearance values for the Koup and Jusko method resulted in somewhat better correlations between expected and observed digoxin concentrations.

**CREATION OF A DOSING NOMOGRAM**

From our data set and the resulting regression equation, a simple nomogram was constructed for use by clinicians in determining the initial dose of digoxin in heart failure (target concentration, 0.7 ng/mL [0.9 nmol/L]). This nomogram is shown in Figure 2. A given patient’s recommended digoxin dose can be estimated by plotting their creatinine clearance (x-axis) by either their IBW (y-axis) or their height (z-axis) because IBW is a function of height and is not often calculated by most clinicians. As displayed in the nomogram, digoxin dose increases linearly with increasing creatinine clearance and increasing IBW (or increasing height).

**COMMENT**

Our intention in this study was to create a practical way of determining the proper dosage of digoxin when given for patients with systolic heart failure. This was done given new information that implied improved mortality with digoxin concentrations of 0.5 to 0.9 ng/mL (0.6-1.2 nmol/L), a range narrower and lower than the range historically used (0.8-2.0 ng/mL [1.0-2.6 nmol/L]). Although the Jelliffe method was used in the Digitalis Investigation Group trial, our sense is that most clinicians have abandoned previously published methods to determine the dosage of digoxin, perhaps because they are too cumbersome. Therefore we constructed and herein offer a nomogram wherein only estimated creatinine clearance and IBW or height are necessary to pick an initial dose of digoxin designed to achieve a steady state concentration of 0.7 ng/mL (0.9 nmol/L).
By using the proposed nomogram shown in Figure 2, most patients will require daily digoxin doses of either 0.125 mg or 0.0625 mg (0.125 mg every other day), which is lower than those recommended by existing dosing methods. In most of the 0.25-mg zone of the nomogram (particularly the lower portion), the clinician could rationally decide to begin with alternating daily doses of 0.125 and 0.25 mg of digoxin (as shown by the gradual shading in this area). However, to many this is a confusing regimen that could lead to dosing errors and possibly digoxin toxicity.21

After the nomogram was constructed, we compared the prescribed digoxin dose with that recommended by our dosing nomogram and, in turn, analyzed the resultant serum digoxin concentrations. Of the 54 patients, 33 (61%) had digoxin concentrations of 0.5 to 0.9 ng/mL (0.6-1.2 nmol/L) in the data set and similarly, 33 (65%) of 51 patients would have had concentrations within this range using our nomogram. However, of the 54 patients in the data set, 19 (35%) had digoxin concentrations greater than 1.0 ng/mL (>1.3 mmol/L) whereas only 11 (22%) of 51 would have had concentrations greater than 1.0 ng/mL (>1.3 mmol/L) if dosed according to the proposed method. Alternatively, recent guidelines9 suggest the digoxin concentration should be less than 1.0 ng/mL (<1.3 nmol/L) in patients with heart failure. Using this as a goal, of the 54 patients in the data set, 40 (78%) of 51 patients would have had digoxin concentrations less than 1.0 ng/mL (<1.3 nmol/L) whereas with the doses recommended by the proposed nomogram, it was estimated that 40 (78%) of 51 patients would have had digoxin concentrations less than 1.0 ng/mL (<1.3 mmol/L). These data suggest a tendency for the dose recommended by our proposed nomogram to less frequently result in undesirable higher concentrations (>1.0 ng/mL [>1.3 mmol/L]) compared with those in our data set, perhaps reflecting “usual medical care.” However, comparisons of this type would be better served by a prospective randomized trial with a larger sample size.

Our method was more precise (using RMS) in predicting the patient’s digoxin concentration than the Jelliffe method and somewhat more precise (although not statistically distinct) than the Koup and Jusko method. Although the Jelliffe method was originally designed to result in a concentration of about 1.4 ng/mL (1.8 nmol/L), both of the older methods can be adapted to estimate a dose of digoxin that would result in an expected digoxin concentration of 0.7 ng/mL (0.9 mmol/L). The Koup and Jusko method (particularly when using heart failure digoxin clearance values) was more precise than the Jelliffe method. This finding is similar to Koup and Jusko’s original observations in which their method performed better than a method similar to Jelliffe’s, which gives us a degree of confidence in our data set (despite the retrospective nature of the data collection). Using the Koup and Jusko method (for heart failure patients) and a target digoxin concentration of 0.7 ng/mL (0.9 mmol/L), one can develop dosing suggestions based on the patient’s renal function. They are as follows, based on creatinine clearance (according to Cockcroft and Gault22) values:

- Less than 30 mL/min (<0.5 mL/s): start at 0.125 mg every other day
- 30 to 80 mL/min (0.5-1.3 mL/s): start at 0.125 mg every day
- 80 to 120 mL/min (1.3-2.0 mL/s): start at 0.25 mg alternating with 0.125 mg every day
- Greater than 120 mL/min (>2.0 mL/s): start at 0.25 mg every day

The median dose of digoxin in the Digitalis Investigation Group trial was 0.25 mg/d.11 Because of the more recent emphasis on using lower maintenance doses of digoxin, one could consider empirically an initial treatment of 0.125 mg/d of digoxin in nearly all patients with heart failure.2 However, according to our results, most patients (depending on height or IBW) with even moderate (stage 3) renal insufficiency (creatinine clearance, <60 mL/min [<1.0 mL/s]) should receive 0.125 mg of digoxin every other day. In the Digitalis Investigation Group trial,22 46% of patients enrolled had glomerular filtration rates of less than 60 mL/min per 1.73 m². Hence, given the importance of maintaining the digoxin concentration within the narrow window associated with improved mortality, we propose using our dosing guidelines to determine the initial dose of digoxin. Subsequently, the digoxin concentration should be monitored and the dose of digoxin adjusted to ensure that the chronic steady state dose results in trough concentrations of 0.5 to 0.9 ng/mL (0.6-1.2 nmol/L).

One additional point in this regard could be made. Digoxin tablets are the most commonly prescribed dosage form but are available only in 0.125- and 0.25-mg strengths. Our results and the need to perhaps be more precise in tailoring chronic dosing regimens to obtain therapeutic concentrations should prompt the availability of new strengths, such as 0.0625- and 0.1875-mg tablets.

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REFERENCES