CAN DIGOXIN DOSE REQUIREMENTS BE PREDICTED?

SYLVIA M. DOBBS, G.E. MAWER, ELAINE M. RODGERS & B.G. WOODCOCK

Department of Pharmacology, Materia Medica and Therapeutics, University of Manchester, Manchester M13 9PT

S.B. LUCAS

Department of Physics and Mathematics, Preston Polytechnic, Preston

- 1 A search for patient variables relevant to digoxin dose requirements was made in forty-three patients with a wide range of renal and hepatic function. The daily dose of digoxin to achieve a mean serum concentration of 1.5 ng/ml, the standardized dose, was calculated for each patient.
- 2 The standardized dose correlated significantly with the following variables, in descending order of correlation coefficient; creatinine clearance, serum creatinine concentration, body weight and serum albumin concentration. An equation containing the two independent variables, creatinine clearance and serum albumin concentration, had a significantly stronger correlation with standardized dose than creatinine clearance alone.
- 3 Attempts were made in each patient to predict the standardized dose using both empirical prescribing methods and the published nomograms. Although a maximum of 70% of the variance of the standardized dose was explained, this corresponded approximately to one patient in three having a predicted dose outside the 95% confidence limits for the standardized dose.
- 4 There remain important sources of individual variation in digoxin dose requirements yet to be identified. Future application of empirical prescribing methods, such as multiple linear regression and Bayes' theorem, to prescription for large, defined patient groups may improve dose prediction for individual patients.

Introduction

There are several factors which make prediction of maintenance digoxin dose requirements a problem. The therapeutic effect of digoxin, particularly the positive inotropism in sinus rhythm (Shapiro, Narahara & Taubert, 1970) is often difficult to quantify, and may be masked by other treatment. Toxic side effects may be confused with the condition being treated. Single serum digoxin assays are of limited value since there is considerable overlap between therapeutic and toxic serum concentrations (Chamberlain, White, Howard & Smith, 1970). Although clinical judgement is relevant to the determination of the correct dose for a given patient, the high incidence of digoxin toxicity reported by Carruthers, Kelly & McDevitt (1974) suggests the need for a method of avoiding excessive maintenance dose prescription.

Nomograms for digoxin dosage have been developed by Dettli, Spring & Ryter (1971), and Jelliffe & Brooker (1974). They are based on the

assumption that dose and renal function, together with weight in the case of Jelliffe's nomogram, are the major determinants of the serum digoxin concentration/time curve. Assessment of the nomograms in terms of the percentage variance of serum digoxin concentration accounted for can be misleading, unless the variability of the relevant patient groups is considered. Jelliffe, Buell & Kalaba (1972) accounted for 74% of the variance in serum digoxin concentration in a patient group with a wide range of renal function. However Peck, Sheiner, Martin, Combs & Melmon (1973), and Wagner, Yates, Willis, Sakinar & Stoll (1974), using variables including renal function and body weight, accounted for less than 35% of the variance in digoxin concentration in patients with normal or only slightly impaired renal function. They concluded that other unidentified patient variables are relevant to digoxin dosage.

We present the results of a search for relevant variables in a group of patients, not only with a

wide range of renal function, but also of hepatic function, diagnosis, body weight and age. Empirical methods of prescribing for the group are explored. The relative efficacy of prescribing methods is determined by the proportion of patients for which the correct dose, as defined below, is prescribed.

Methods

Digoxin preparation

The study was restricted to a single brand of digoxin tablets (Lanoxin, 62.5 and 250 µg, Wellcome Medical Division).

Prediction of creatinine clearance in patients with cardiac failure

An initial study was made of the relationship between measured creatinine clearance and the corresponding predicted creatinine clearance based on the data of Siersbaek-Nielsen, Hansen, Kampmann & Kristensen (1971). Fifty-one patients receiving digoxin were studied. The measured creatinine clearance was calculated from a minimum of two estimates of serum creatinine concentration and the corresponding 24 h urinary excretion of creatinine. The patient variables used in the prediction of creatinine clearance were the mean serum creatinine concentration, age, sex and body weight.

An index of cardiac failure was calculated at every patient visit, scoring for clinical signs as shown in Table 1. In the majority of patients the score remained constant. Where the score varied a mean value was taken.

Patients receiving maintenance digoxin therapy

It was assumed that a steady state condition with respect to serum digoxin concentrations was

Table 1 Scoring criteria for cardiac failure

<i>Clinical sign</i>	<i>Score</i>		
	<i>0</i>	<i>1</i>	<i>2</i>
1 Jugular venous pressure (distance above manubrium sterni when inclined at 45°)	<2 cm	2 cm to angle of jaw	Above angle of jaw
2 Oedema	Absent	Moderate	Gross
3 Distance (finger widths) of tender liver edge below costal margin	<1	1-2	3 or more
4 Systolic blood pressure (mmHg)	100 or greater	<100	
5 Cold extremities	Absent	Present	
Index of cardiac failure	Sum of the scores for clinical signs 1, 2, 3, 4 and 5		

Table 2 Characteristics of patients studied

Characteristic	Mean	Range	s.d.
Weight (kg)	61.0	36.4-87.0	12.3
Age (years)	56.1	25.0-83.0	16.9
Serum creatinine concentration (mg/100 ml)	3.1	0.6-20.3	4.6
Creatinine clearance (ml/min)*	52.0	0.4-152.1	36.9
Serum albumin concentration (mg/100 ml)	3.9	2.5-4.9	0.5
Serum globulin concentration (mg/100 ml)	3.1	1.7-4.8	0.6
Serum bilirubin concentration (mg/100 ml)	0.7	0.2-2.4	0.5
Serum alkaline phosphatase (K.A. units/100 ml)	16.5	1.4-61.0	11.5
Cardiac failure score	2.8	0-8	
Digoxin dose (µg/day) administered	196	62.5-500	109
Mean digoxin concentration in steady state (ng/ml)	1.19	0.56-2.38	0.53
Calculated digoxin dose (µg/day) for mean concentration of 1.5 ng/ml	280	59-758	168

* Predicted creatinine clearance, except in patients with severe cardiac failure when measured creatinine clearance was used (see results section).

attained in 3 weeks if the daily maintenance dose was fixed and the serum creatinine concentration stable. Forty-three (twenty-eight male, fifteen female) of the patients met these requirements; the remainder were excluded from the study. Both inpatients and outpatients were included. The characteristics of the patients studied are shown in Table 2.

Samples of venous blood were taken for digoxin assay on a minimum of two occasions in each patient. The samples were taken immediately before and 6 h after a dose.

Digoxin assay

The blood samples were kept at 4°C for not more than 48 h before the serum was removed. This was then assayed immediately or stored in separate 1 ml aliquots at -10°C for up to 1 month. Preliminary work showed that serum could be stored for at least 1 week at 4°C, and for several months at -10°C, without detectable change in digoxin concentration.

The digoxin concentrations were determined by radioimmunoassay using a commercial kit (Lanoxitest β , Wellcome Reagents Ltd) based upon the [^3H]-digoxin, charcoal separation method of Smith, Butler & Haber (1969). The patients had not been given radioisotopes, spironolactone or digitoxin. Since the method does not distinguish between free and protein bound digoxin, the assay values refer to total digoxin in serum.

The calibration curve covered the range 0.4 ng/ml and was based upon triplicate estimations of six data points. Standards and two replicates of each serum sample were assayed using a protocol designed to minimize systematic errors. An empirical quality control scheme (Woodcock, Rodgers & Gibbs, 1975) was used to determine the precision of the assay and monitor its stability.

The between assay coefficient of variation of a serum sample assayed in duplicate was 11% ($n = 13$) at 0.8 ng/ml and 8% ($n = 13$) at 1.9 ng/ml.

Determination of the standardized dose

The calculated dose D_i ($\mu\text{g/day}$) for a mean steady state serum digoxin concentration of 1.5 ng/ml in patient i ($i = 1, 2$ to 43), was termed the standardized dose. This concentration is consistent with the midpoint of the therapeutic ranges suggested by the studies of Chamberlain *et al.* (1970), Evered, Chapman & Hayter (1970), and Smith & Haber (1970).

The mean, C_i , of the serum digoxin concentrations just before and 6 h after the given

daily dose, G_i ($\mu\text{g/day}$), was taken as an estimate of the mean serum concentration achieved. Then assuming, in each patient, that the mean steady state concentration achieved was directly proportional to daily dose, the 95% confidence limits of D_i were calculated by $D_i = 1.5 G_i / (\bar{C}_i \pm 2 \text{ s.e. mean})$, where $\bar{C}_i$ is the mean of the available values of C_i , and s.e. mean is the standard error of $\bar{C}_i$. For patient i the error variance of $\bar{C}_i$ was estimated by dividing the mean within patient variance of C_i , by n , where n is the number of values of C_i obtained in this patient. In the majority of patients $n = 1$ and the confidence limits approximated to 75% and 150% of the standardized dose. In assessment of the prescribing methods the individual confidence limits were used.

Linear regression

Simple correlation coefficients were calculated between each of the parametric patient variables X_{ij} (for variables $j = 1, 2$ to m) and the standardized dose D_i . A best fitting linear regression equation was calculated using the variable (X_{i1}) with the highest correlation coefficient:

$D_i = b_0 + b_1 X_{i1}$, where b_0 is a constant, and b_1 the regression coefficient.

Multiple linear regression

An ICL computer program was used. The equation for m independent variables was $D_i = b_0 + b_1 X_{i1} + \dots + b_j X_{ij} + \dots + b_m X_{im}$, where b_j is the regression coefficient of the j^{th} independent variable. The equation selected contained the set of variables which had the most significant partial correlation coefficients with D_i .

Bayes' theorem

Bayes' theorem has been used by several workers to assist diagnosis (Warner, Toronto, Veasy & Stephenson, 1961; Burbank, 1969; Taylor, 1970; Knill-Jones, Stern, Grimes, Maxwell, Thompson & Williams, 1973), but has not previously been used to assist prescribing. The problem of prescribing the correct dose for a patient is analogous to the problem of assigning the correct diagnosis: in each case using a set of attributes the patient is assigned to a particular class. The attributes are the clinical and laboratory characteristics of the patient. Class refers to disease in the case of diagnosis and to dose in prescribing.

The dose, expressed in multiples of 62.5 μg , which would achieve the mean steady state serum

digoxin concentration closest to 1.5 ng/ml in patient i was called the appropriate dose.

In the event S_i that a patient i has a given set of observed independent variables, then by Bayes' theorem the probability that D_k ($k = 1, 2$ to z) is the appropriate dose, from an exhaustive set of z mutually exclusive doses is given by:

$$p_i(D_k/S_i) = \frac{p_i(S_i/D_k) \cdot p(D_k)}{p_i(S_i/D_k) \cdot p(D_k) + p_i(S_i/\bar{D}_k) \cdot p(\bar{D}_k)}$$

where $p_i(S_i/D_k)$ is the probability of observing S_i when D_k is the appropriate dose for patient i .

$p(D_k)$ is the probability that D_k is the appropriate dose for any patient,

$p_i(S_i/\bar{D}_k)$ is the probability that S_i will be observed when D_k is not the appropriate dose for the patient i and

$p(\bar{D}_k)$ is the probability that D_k is not the appropriate dose for any patient.

The probabilities were calculated from the observed relative frequencies of the events. This calculation ideally requires larger patient numbers than were available in the present study.

Nomograms

The standardized dose D_i ($\mu\text{g/day}$) for each patient was compared with the dose Q_i ($\mu\text{g/day}$) prescribed for that patient by the available nomograms.

According to Dettli, Spring & Ryter (1971) Q_i is proportional to the elimination rate constant which can be obtained by substitution of the creatinine clearance, CCr_i , into a single regression equation (Dettli, Ohnhaus & Spring, 1972). Assuming standardized dose of $517 \mu\text{g/day}$ when CCr_i is 120 ml/min (see Results, regression of D_i on CCr_i), the Dettli method gives $Q_i = 3.12 CCr_i + 143$.

The nomogram of Jelliffe & Brooker (1974) refers to a serum concentration 6 h after a dose. It also gives digoxin half times for different values of CCr_i . This enabled us to calculate for each patient the 6 h concentration corresponding with a

mean concentration of 1.5 ng/ml. Failure to make the adjustment would have exaggerated the tendency of the nomogram to underprescribe for many of our patients (see Results).

Results

Prediction of creatinine clearance

The predicted creatinine clearance was not valid for patients with gross right-sided failure (a total score of at least 4 for clinical signs 1, 2 and 3 in Table 1), or with a low cardiac output state (a score of at least 1 for signs 4 and 5) (Table 3). In the following description therefore creatinine clearance, CCr_i , refers to the measured value in these patients and to the more convenient predicted value in the remainder.

Linear regression

The correlation between the standardized dose D_i ($\mu\text{g/day}$) and single patient variables is shown in Table 4. Creatinine clearance showed the strongest correlation and the corresponding regression equation was:

$$D_i = 3.56 CCr_i + 93.0 \mu\text{g/day}$$

Serum creatinine concentration, body weight and serum albumin were correlated significantly with standardized dose but not with each other. These variables and the non-parametric variable, the cardiac failure index, were used in the application of Bayes' theorem.

Multiple linear regression

The two variables having the most significant partial correlation with the standardized dose were creatinine clearance and serum albumin concentration (Table 5). The regression equation using these two independent variables was:

$$D_i = 3.45 CCr_i + 27.0 A_i \mu\text{g/day}$$

Table 3 Failure to predict creatinine clearance in patients with severe cardiac failure

Degree of cardiac failure	Number of patients	Creatinine clearance (ml/min $\pm$ s.e. mean)		Paired t-test	
		Measured	Predicted	t	P
Severe*	20	34.5 $\pm$ 8.5	46.6 $\pm$ 10.5	3.1	<0.01
Less than severe	31	55.2 $\pm$ 6.5	55.4 $\pm$ 6.8	0.1	>0.9

* Total score of >4 for clinical signs 1, 2 and 3, or of at least 1 for signs 4 and 5 (Table 1).

Table 4 Correlation between the standardized daily dose ($\mu\text{g/day}$) of digoxin and single variables in forty-three patients

Variable	Correlation coefficient	
	r	P
Creatinine clearance	0.83	<0.001
Serum creatinine concentration	-0.51	<0.001
Serum albumin concentration	0.45	<0.005
Weight	0.45	<0.005
Serum alkaline phosphatase	0.37	<0.02
Serum globulin	0.28	>0.05
Age	-0.24	>0.10
Serum bilirubin	0.03	>0.80

Table 5 Correlation between the standardized daily dose ($\mu\text{g/day}$) of digoxin and a set of variables in forty-three patients

Variable	Partial correlation coefficient	
		P
Creatinine clearance	0.80	<0.001
Serum albumin	0.55	<0.001
Serum alkaline phosphatase	0.36	<0.05
Serum globulin	-0.19	>0.20
Age	-0.08	>0.60
Bilirubin	-0.05	>0.70
Weight	-0.02	>0.90

Table 6 The frequency with which the standardized dose ($\mu\text{g/day}$) of digoxin was predicted in forty-three patients using nomograms and empirical relationships between dose and patient variables

Prediction method		Predicted dose			r	100r ² %
		Within 95% confidence limits				
		Too small		Too large		
Empirical	1 Linear regression equation	7	28	8	0.82	67
	2 Multiple linear regression equation	4	30	9	0.84	70
	3 Application of Bayes' theorem	13	26	4	*	
Nomogram	4 Dettli	3	27	13	0.78	62
	5 Jelliffe	18	23	2	0.77	59
	6 Expected result if no prediction error	1	41	1		

r correlation coefficient of predicted standardized dose against 'observed' standardized dose

* non-parametric method

where A_i is the serum albumin concentration of patient i .

Comparison of prescribing methods

The ability of the empirical methods and the nomograms to predict D_i are shown in Table 6. The number of patients with predicted doses within the 95% confidence limits of D_i is given for each method. The Chi-squared test revealed a highly significant difference between the result expected if there was no prediction error and those obtained by both empirical and nomogram approaches (Table 7). There was no significant difference between the predictive abilities of the

empirical methods and Dettli's nomogram, nor between Jelliffe's nomogram and the application of Bayes' theorem.

The linear and multiple linear regression equations accounted for the highest percentage of the variance of the standardized dose.

Overprediction of dose in severe cardiac failure

Using both linear and multiple linear regression equations, five of the fourteen patients with severe cardiac failure had predicted doses above the 95% confidence interval for standardized dose ($P < 0.05$, Fisher's exact probability test, Tocher's modification).

Table 7 Significance of above results using Chi-squared test

Methods compared (referred to by number)	χ^2	d.f.	P
1, 2, 3, 4, 5, 6	52.1	10	<0.001
1, 2, 3, 4, 5	29.4	8	<0.001
1, 2, 4	3.4	4	>0.50
1, 2, 4, 6	18.6	6	<0.005
3, 5	0.8	2	>0.50
3, 5, 6	22.5	4	<0.0005

Discussion

The work of Shapiro and co-workers (1970), Bertler, Bergdahl & Karlsson (1974), and Schoenwald (1974) suggests that the response to digoxin administration is dependent upon the concentration achieved in the tissue compartment. Without determining the pharmacokinetic constants for each patient, the best available guide to the mean tissue concentration achieved is the area under the serum concentration/time curve during a maintenance dose interval. This area is proportional to the mean steady state serum concentration if the dosage interval is constant. In the present study the dose to achieve a given mean steady state serum concentration was chosen as the parameter against which to assess the predictive value of patient variables. The optimum mean steady state serum concentration for the population was accepted as 1.5 ng/ml.

In the heterogeneous group of patients studied, the patient variables used in the nomograms of Dettli and co-workers (1971) and Jelliffe & Brooker (1974) correlated significantly with the standardized dose. Creatinine clearance had a stronger correlation with the standardized dose than either body weight alone, or an expression containing both creatinine clearance and weight as independent variables.

A further patient variable, serum albumin concentration, was found to have significant direct and partial correlation with the standardized dose. However there was no significant difference between the multiple linear regression equation containing both creatinine clearance and serum albumin concentration and the simple creatinine clearance regression equation in terms of the number of patients with predicted doses within the 95% confidence limits for the standardized dose.

A non-parametric variable, the semiquantitative index of cardiac failure, was found relevant to the prediction of the standardized dose. A significant number of patients with severe cardiac failure, as defined by an index of cardiac failure >4, had excessive doses predicted by the empirical regression equations, despite the use of measured, in place of predicted, creatinine clearance. This is consistent with the findings of Peck and co-workers (1973).

The nomograms of Dettli *et al.* (1971) and Jelliffe & Brooker (1974) accounted for 62 and 59% of the variance of the standardized dose in the patient group. Jelliffe restricts the use of his nomogram to patients with 'reasonably normal' hepatic function. Observing this restriction did not produce an improvement in correlation between the standardized dose and its predicted value ($r = 0.77$ in each case).

The equations derived empirically from the patient data explained a maximum of 70% of the variance of the standardized dose. This corresponded approximately to one patient in three having a predicted dose outside the 95% confidence interval for the standardized dose (Table 6): the standardized dose for an individual could not be predicted with confidence, even using formulae empirically derived from the patient group. None of the prescribing methods studied showed a significant improvement over the predictive value of the creatinine clearance regression equation (Fisher's Z test, $P = 0.102$).

The future study of defined patient groups may reveal other variables on which the standardized dose depends. Variability of digoxin absorption (Johnson & Bye, 1975) and patient compliance (Sheiner, Rosenberg, Marathe & Peck, 1974) may be important factors. The application of Bayes' theorem, given adequate patient numbers, has the potential advantage of combining both parametric and non-parametric variables in the prediction of dose.

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References

- BERTLER, A., BERGDAHL, B. & KARLSSON, E. (1974). Plasma-digoxin concentrations after an intravenous loading dose. *Lancet*, ii, 958.
- BLOOM, P.M., NELP, W.B. & TUELL, S.H. (1966). Relationship of the excretion of tritiated digoxin to renal function. *Am. J. med. Sci.*, 251, 133-144.
- BURBANK, F. (1969). A computer diagnostic system for the diagnosis of prolonged undifferentiating liver disease. *Am. J. Med.*, 46, 401-415.
- CARRUTHERS, S.G., KELLY, J.G. & McDEVITT, D.G. (1974). Plasma digoxin concentrations in patients on admission to hospital. *Br. Heart J.*, 36, 707-712.
- CHAMBERLAIN, D.A., WHITE, R.J., HOWARD, M.R. & SMITH, T.W. (1970). Plasma digoxin concentrations in patients with atrial fibrillation. *Br. med. J.*, 3, 429-432.
- DETLI, L., OHNHAUS, E.E. & SPRING, P. (1972). Digoxin dosage in patients with impaired kidney function. *Br. J. Pharmacol.*, 44, 373P.
- DETLI, L., SPRING, P. & RYTER, S. (1971). Multiple dose kinetics and drug dosage in patients with kidney disease. *Acta Pharmac. Tox.*, 29, suppl. 3, 211-224.
- EVERED, D.C., CHAPMAN, C. & HAYTER, C.J. (1970). Measurement of plasma digoxin concentration by radioimmunoassay. *Br. med. J.*, 3, 427-428.
- JELLIFFE, R.W. & BROOKER, G. (1974). A nomogram for digoxin therapy. *Am. J. Med.*, 57, 63-68.
- JELLIFFE, R.W., BUELL, J. & KALABA, R. (1972). Reduction of digitalis toxicity by computer-assisted glycoside dosage regimens. *Ann. intern. Med.*, 77, 891-906.
- JOHNSON, B.F. & BYE, C. (1975). Maximal intestinal absorption of digoxin and its relation to steady state plasma concentration. *Br. Heart J.*, 37, 203-208.
- KNILL-JONES, R.P., STERN, R.N., GRIMES, D.H., MAXWELL, J.D., THOMPSON, R.P.H. & WILLIAMS, R. (1973). Use of sequential Bayesian Model in diagnosis of jaundice by computer. *Br. med. J.*, 1, 530-533.
- PECK, C.C., SHEINER, L.B., MARTIN, C.M., COMBS, D.T. & MELMON, K.L. (1973). Computer-assisted digoxin therapy. *N. Engl. J. Med.*, 289, 441-446.
- SCHOENWALD, R.D. (1974). Evidence for variable digoxin absorption as estimated by pharmacological response intensities. *J. pharm. Sci.*, 63, 411-416.
- SHAPIRO, W., NARAHARA, K. & TAUBERT, K. (1970). Relationship of plasma digitoxin and digoxin to cardiac response following intravenous digitalization in man. *Circulation*, 42, 1065-1072.
- SHEINER, L.B., ROSENBERG, N., MARATHE, V.V. & PECK, C. (1973). Differences in serum digoxin concentrations between outpatients and inpatients: An effect of compliance. *Clin. Pharmac. Ther.*, 15, 239-246.
- SIERSBAEK-NIELSEN, K., HANSEN, J.M., KAMPMANN, U. & KRISTENSEN, M. (1971). Rapid evaluation of creatinine clearance. *Lancet*, i, 1133-1134.
- SMITH, T.W., BUTLER, V.P. Jr. & HABER, E. (1969). Determination of therapeutic and toxic serum digoxin concentrations by radioimmunoassay. *N. Engl. J. Med.*, 281, 1212-1216.
- SMITH, T.W. & HABER, E. (1970). Digoxin intoxication: the relationship of clinical presentation to serum digoxin concentration. *J. clin. Invest.*, 49, 2377-2386.
- TAYLOR, T.R. (1970). Computer-guided diagnosis. *J. Roy. Coll. Physicians, Lond.*, 4, 188-195.
- WAGNER, J.G., YATES, J.D., WILLIS, P.W., SAKMAR, E. & STOLL, R.G. (1974). Correlation of plasma levels of digoxin in cardiac patients with dose and measures of renal function. *Clin. Pharmac. Ther.*, 15, 291-301.
- WARNER, H.R., TORONTO, A.F., VEASY, G. & STEPHENSON, R.A. (1961). A mathematical approach to medical diagnosis. Application to congenital heart disease. *J. Am. med. Ass.*, 177, 177-183.
- WOODCOCK, B.G., RODGERS, E.M. & GIBBS, A.C. (1975). Quality control of digoxin radioimmunoassay. *Proceedings of the radioimmunoassay symposium*, Oxford, 24th-26th Sept. 1974, London: Heyden & Son Ltd.

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