A score for prescribing digoxin

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SUMMARY A simple method of selecting a maintenance dose of digoxin, suitable for an adult patient, was derived from data on 129 patients taking digoxin. Eight items of readily available information are required for entry into the prescribing aid: out/inpatient status, sex, age (less/not less than 70 years), weight (allocated to one of four ranges), whether or not chronically house/chair bound, cardiac rhythm (sinus/other), serum creatinine concentration (allocated to one of four ranges), and diuretic therapy (prescribed/not prescribed). The recommended dose is given in terms of size and number of tablets to be prescribed. Using this method 72.3 per cent of patients are expected to achieve mean steady state serum digoxin concentrations within the therapeutic range, 6.5 per cent above and 21.2 per cent below. This performance would be considerably better than that expected from the use of other prescribing aids. If available, routine measurement of the serum digoxin concentration during follow-up is recommended to detect those who might benefit from a change, usually an increase, in dose.

Although, ideally, the dose of digoxin should be chosen by titration against response, this may be difficult. Rapid ventricular rates in atrial fibrillation do not always respond to digoxin, and evaluation of the inotropic effect may be confounded by response to other interventions. Moreover the less serious manifestations of toxicity, such as nausea, anorexia, and fatigue, do not serve as a reliable warning of cardiotoxicity.

Measurement of the serum digoxin concentration has proved of use in choosing the dose for individual patients (Sheiner, 1974). Redfors (1972) defined an optimal serum concentration for long-term control of atrial fibrillation, and sustained inotropic effect has been shown at a similar concentration in patients in sinus rhythm (Dobbs *et al.*, 1977a). Smith and Haber (1970) defined a ceiling concentration below which the risk of cardiotoxicity was small. However, in practice, the value of the assay is limited by its restricted availability and by delays in receiving results. We describe a simple method for prescribing digoxin based on readily available information.

Patients and methods

One hundred and twenty-nine patients (110 outpatients and 19 inpatients; 67 men and 62 women)

receiving maintenance digoxin agreed to take part in the study. The mean age (± 1 SD) was 59 ± 12 years, mean weight 62 ± 13 kg, and mean creatinine clearance 60 ± 23 ml/min.

At the first interview the previous supply of digoxin tablets was collected and an equivalent daily dose of 'Lanoxin' dispensed. Having allowed at least three weeks for 'steady state' (Wagner *et al.*, 1965) conditions to be attained, venous blood samples for digoxin assay were taken on an average of four occasions per patient. Blood was sampled immediately before a daily dose (10 am). The mean steady state serum concentration, $\bar{C}$ nmol/l, was estimated from the predose concentration, C_0 nmol/l, using the equation $\bar{C} = 0.37 + 1.08 C_0$ (Dobbs *et al.*, 1976c). In 14 patients this equation was not applicable because of poor renal function, so the concentration 6 hours after the daily dose was taken as a direct measure of the mean steady state concentration (Dobbs *et al.*, 1976c).

Patients and relatives, or nursing staff, were questioned about compliance and encouraged to ensure that tablets were taken as prescribed. Compliance was further encouraged in 86 of the outpatients by dispensing tablets in calendar packs and counting surplus tablets at each visit.

DIGOXIN ASSAY

Serum digoxin concentrations were measured by radioimmunoassay (Lanoxitest β , Wellcome Re-

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agents Ltd.). The between assay coefficient of variation of a serum sample assayed in duplicate was 10 per cent at a concentration of 1.3 nmol/l and of 2.6 nmol/l.

PATIENT CHARACTERISTICS

The following were recorded for each patient: out/inpatient status, sex, age, weight, height, biacromial and bitrochanteric diameters, mobility (whether chronically house- or chair-bound or not), and previous history with respect to renal disease. The patients were graded according to their symptoms and signs of cardiac disease (Dobbs *et al.*, 1977a) and questioned about other drugs taken with special reference to diuretics, antacids (Binnion and McDermott, 1972), and purgatives (Manninen *et al.*, 1973). Endogenous creatinine clearance was measured and, in addition, a prediction of creatinine clearance was made from age, sex, weight, and serum creatinine concentration using the nomogram of Siersbaek-Nielsen *et al.* (1971).

In the 86 patients, to whom digoxin was dispensed in calendar packs, the clinical assessment was made by a doctor unaware of the patient's digoxin dose. Additional biochemical investigations were made in this group: blood urea, serum uric acid, sodium, potassium, calcium, bicarbonate, chloride, albumin, globulin, alkaline phosphatase, bilirubin, aspartate aminotransferase, alanine aminotransferase, hydroxybutyric dehydrogenase, γ -glutamyl transpeptidase, and the haemoglobin concentration.

ANALYSIS

A target mean steady state concentration of 1.6 nmol/l, within the lower part of the published therapeutic range (Chamberlain *et al.*, 1970; Smith and Haber, 1970) (1.28-2.56 nmol/l), and close to Redfors' (1972) optimum, was selected. The dose required by each patient to achieve this target, 'the dose requirement', was calculated assuming proportionality between the amount of digoxin given daily to an individual and the mean concentration achieved (Wagner *et al.*, 1965; Dobbs *et al.*, 1976b).

Multiple linear regression analysis (Nie *et al.*, 1975) was used to examine the effect of patient characteristics on the logarithm of the dose requirement (for explanation of need for log transformation see Appendix). Use of this technique presumes that the variation in the dependent variable, y (in this case $\log_{10}$ (dose requirement)), can be accounted for by a linear equation containing independent variables $x_1, x_2, \dots, x_k$ (the patient characteristics), and a residual error, E : $y = b_0 + b_1x_1 + b_2x_2 + \dots + b_kx_k + E$. The sum of squares of the values of y

about the mean (total sum of squares), representing the original variation in y , may be partitioned into a regression sum of squares, the variation explained by the equation, and the residual sum of squares the unexplained variation. Coefficients, $b_0, b_1, b_2, \dots, b_k$, are chosen to give a minimum residual sum of squares. The ratio (regression sum of squares)/(total sum of squares), ' R^2 ', may be used as an estimate of how much of the original variation in y has been explained by the equation. However, this is an optimistic estimate and we prefer the 'adjusted R^2 ' described in the Appendix.

The best subset containing k characteristics may be selected from the many available characteristics using the stepwise method (Nie *et al.*, 1975). The characteristic giving the largest value of R^2 is adopted as x_1 . Each of the remaining characteristics is then tried, one at a time, as x_2 in an equation already containing x_1 , and the characteristic which gives the largest increment in R^2 is retained as x_2 . This procedure is then repeated for x_3 to x_k .

Results

EVALUATION OF BIOCHEMICAL INFORMATION IN PRESCRIBING

In 86 of the outpatients, 30 clinical characteristics (including 3 'complex' ones: body surface area (Du Bois and Du Bois, 1916), estimated lean body mass (Behnke, 1969), and a cardiac failure score (Dobbs *et al.*, 1976a)), and 20 biochemical characteristics (including measured and predicted (Siersbaek-Nielsen *et al.*, 1971) creatinine clearance and albumin/globulin ratio) were recorded. Since clinical information is more readily available than biochemical, we compared our ability to predict dose requirement using only clinical information with that using information from both sources (Table 1). Certain biochemical characteristics, added singly to an equation containing clinical data, improved the prediction, the best of these being the reciprocal of the serum creatinine concentration. The inclusion of further biochemical information was then of little advantage.

Table 1 Comparison of maximum adjusted R^2 obtained by stepwise regression using different groupings of characteristics in 86 patients

Nature of characteristics (number in group)	Maximum adjusted R^2
Clinical (30)	0.51
Clinical (30) and reciprocal of serum creatinine concentration	0.63
Clinical (30) and biochemical (20)	0.67

Table 2 Multiple linear regression equation for prediction of digoxin dose requirement in adult patients

Log_{10} (dose requirement in mg) = $0.2057A + 0.0608B + 0.5443C + 0.1429D + 0.0840E - 0.0974F - 0.0481G - 0.0490H - 1.5141$
 where the patient characteristics, their codings and the corresponding F values are as follows:

Characteristic	Coding	F	P (n = 129)
(A) In/outpatient	A = 1 for inpatients, 2 for outpatients	36.2	< 0.001
(B) Weight	B = 1 below 55.0 kg, 2 for 55.0 to 64.9 kg, 3 for 65.0 to 74.9 kg, and 4 for 75.0 kg and above	30.5	< 0.001
(C) Reciprocal of serum creatinine concentration	C = 1 below 70 $\mu\text{mol/l}$, 1/2 for 70 to 99 $\mu\text{mol/l}$, 1/3 for 100 to 199 $\mu\text{mol/l}$ and 1/4 for 200 $\mu\text{mol/l}$ and above	56.7	< 0.001
(D) Mobility	D = 1 for chronically house/chair bound, and 2 for others	22.6	< 0.001
(E) Sex	E = 1 for females and 2 for males	12.5	< 0.001
(F) Age	F = 1 below 70 years and 2 for 70 years and above	11.5	< 0.001
(G) Heart rhythm	G = 1 for sinus rhythm, and 2 for other rhythms	5.1	< 0.03
(H) Diuretic treatment	H = 1 when not prescribed, and 2 when prescribed	4.8	< 0.03

COMPARISON OF INPATIENT AND OUTPATIENT DOSE REQUIREMENTS

An equation based on the clinical characteristics and the reciprocal of the serum creatinine concentration of the 86 outpatients, was used to predict the dose requirements of the remaining patients. This equation predicted accurately the requirements of the 24 outpatients, but those of the 19 inpatients were overpredicted (Sheiner *et al.*, 1973). Consequently, a 'clinical' characteristic, with one score for inpatients and another for outpatients, was used in further analysis.

FORMULATION OF A PRESCRIBING AID

Stepwise selection was then made from the clinical characteristics together with the reciprocal of the serum creatinine concentration in all 129 patients. Eight characteristics were each associated with a significant reduction in the residual sum of squares (F-test) when added to the regression equation in a separate step, after the others had been included. The predictive value of the set of 8 characteristics was only marginally reduced by coding those measured on a continuous scale (weight, reciprocal of serum creatinine concentration, and age). The 'final' equation is given in Table 2.

COMPARISON WITH OTHER PRESCRIBING AIDS

Residual variance is an index of the difference between predicted and observed dose requirements and is minimal when the mean predicted log dose equals the mean observed log dose. A simple but inaccurate method of prescribing would be to give a dose corresponding to the latter to all patients (0.23 mg for our patients) (Table 3). The nomogram of Jelliffe and Brooker (1974) underpredicted the dose requirements of our patients while the method of Dettli *et al.* (see Dobbs *et al.*, 1976a) overpredicted it. We then modified these aids to give a mean predicted log dose equal to the mean observed in our patients, but the residual variance

Table 3 Comparison of prescribing methods

Prescribing method	Residual variance in log (dose requirement in mg)
Fixed daily dose of 0.23 mg	4.15×10^{-2}
Jelliffe and Brooker (1974) nomogram	Original 3.51×10^{-2} Modified* 2.63×10^{-2}
Dettli <i>et al.</i> method (see Dobbs <i>et al.</i> , 1976a)	Original 4.44×10^{-2} Modified** 2.33×10^{-2}

*Predicted doses multiplied by 1.33.

**Predicted doses multiplied by 0.77.

Residual variance in log (dose requirement in mg) if our final equation were used in a future patient would be expected to be within 95 per cent confidence limits: 1.14×10^{-2} to 1.90×10^{-2} (see Appendix). The table gives residual variances obtained when alternative prescribing methods were used in our patients

was still significantly greater than that estimated for the use of our equation (Table 3).

PRACTICAL APPLICATION

So far it has been assumed that any dose of digoxin can be dispensed. Restricting the predicted doses to practical sizes caused only a slight reduction in the number of patients expected to have mean serum concentrations within the therapeutic range (Table 4).

Calculation of dose requirements using the final equation would require logarithm tables, or preferably a calculator. We, therefore, devised a simplified method (Table 5): a score is allocated to each patient according to the 8 characteristics (step 1); the sum of the 8 scores is then entered into a table and the recommended dose read off (step 2). The use of scores caused only a small increase in the error in prediction (Table 4).

Discussion

The published morbidity associated with digoxin treatment is alarming (Shapiro *et al.*, 1969; Beller *et al.*, 1971). This causes some doctors to use digoxin only for the control of 'rapid' atrial fibrillation. Others ascribe such signs and symptoms to

Table 4 Effects of constraining doses to practical sizes and of simplifying calculation on predictive value of our prescribing method

Constraint on dose	Calculation	Mean steady state serum digoxin concentration (nmol/l)*		
		Too low	Within therapeutic range	Too high
None	Final equation	19.3	75.6	5.1
Practical sizes	Simplified method	21.0	72.7	6.3
		21.2	72.3	6.5

*Percentage of patients expected to have concentrations within therapeutic range is compared (see Appendix)

Table 5a Simple method of calculating digoxin dose
Step 1: Scoring for patient characteristics

Characteristic	Options	Score
Out/Inpatient	Outpatient	..17
	Inpatient	.. 0
Sex	Male	.. 7
	Female	.. 0
Age (y)	Below 70	.. 8
	70 and above	.. 0
Weight (kg)	75 and above	..15
	65.0 to 74.9	..10
	55.0 to 64.9	.. 5
	below 55.0	.. 0
Mobility	Not grossly reduced ..	..12
	Chronically house/chair bound	.. 0
Heart rhythm	Sinus rhythm	.. 4
	Other	.. 0
Serum creatinine concentration (μmol/l)	Below 70	..33
	70 to 99	..11
	100 to 199	.. 4
	200 and above	.. 0
Diuretic treatment	Not prescribed	.. 4
	Prescribed	.. 0
Total score for patient		

Table 5b Step 2: Conversion of score to recommended maintenance dose

Total score	Daily dose (mg)	Tablets prescribed
0-13	0.0625	One 0.0625 mg
14-24	0.09375	One 0.0625 mg/two 0.0625 mg alternate days
25-37	0.125	One 0.125 mg
38-49	0.1875	Three 0.0625 mg
50-61	0.250	One 0.25 mg
62-73	0.375	Three 0.125 mg
74-85	0.500	Two 0.25 mg*
86-100	0.750	Three 0.25 mg*

*Divided between two or three administration times. (Single doses of 0.5 mg or more frequently cause gastrointestinal symptoms shortly after administration.)

the underlying disease or regard benefit as inseparable from toxicity. When it is conceded that a patient may be receiving an inappropriate dose, the doctor is still unlikely to use prescribing aids: even

if he thought them applicable to his patient, he is likely to be deterred by their complexity.

The prescribing aid described was based on a group of patients with widely varying characteristics, who were receiving digoxin tablets conforming with the current dissolution standards. Our ability to predict dose requirements was significantly greater using this method than by using alternatives (Jelliffe and Brooker, 1974; Dobbs *et al.*, 1976a). The risk of achieving mean steady state serum concentrations above the therapeutic range is small using our method, but concentrations below this range are to be expected in one-fifth of cases. (Where a digoxin assay service is available, a single appropriately timed (Dobbs *et al.*, 1976c) blood sample taken during the follow-up period would detect those requiring an alteration in dose.) It is also comparatively simple to use. The need for detailed information about the patient is avoided with only minimal loss of accuracy. In many patients, several of the characteristics will carry a score of zero and so little arithmetic will be required to obtain the total score.

Since, in health, digoxin is excreted mainly by the kidneys, it is not surprising that the characteristics used in the nomogram of Siersbaek-Nielsen *et al.* (1971) for the prediction of creatinine clearance (serum creatinine concentration, weight, sex, and age) were among the 8 characteristics in our final equation. However, since creatinine production depends on muscle mass rather than total body weight, overprediction of creatinine clearance by the nomogram of Siersbaek-Nielsen *et al.* is to be expected in patients who are chronically house- or chair bound and in the grossly obese. This might account for the predictive value of the 'mobility' characteristic in our final equation and the finding that no increase in digoxin dose was necessary for body weights exceeding 75 kg. An equation containing measured creatinine clearance or blood urea concentration (Halkin *et al.*, 1975) instead of serum creatinine concentration gave a poorer prediction of dose requirement, probably as a result of incomplete urine collection and variation in protein intake, respectively.

The 'diuretic treatment' and 'heart rhythm' characteristics made significant contributions to the prediction of dose. These findings are in line with previous work. Dobbs *et al.* (1977a) found that digoxin dose requirement was inversely related to the severity of heart failure, when allowance had been made for differences in serum creatinine concentration, weight, sex, and age. This was partially explained by overprediction of creatinine clearance in these patients, but an increase in tubular reabsorption (Halkin *et al.*, 1975) and/or a reduction

in biliary excretion of digoxin may also occur. Beller *et al.* (1971) found a greater prevalence of atrial fibrillation among patients with digoxin toxicity than those without.

There are several reasons why the out/inpatient characteristic contributed to the predictive value of the final equation. Some inpatients had more pronounced muscle wasting than the outpatients while others had more severe heart failure. Dietary differences may also be important. Fat intake has been shown to bear an inverse relation to dose requirement (Turner *et al.*, 1977): ill inpatients will tend to consume less fat than outpatients. Every effort to achieve maximal compliance was made in our patients. In the 86 outpatients receiving calendar packs, neither counting the tablets nor the history provided evidence of non-compliance. Moreover the equation derived in these outpatients gave accurate predictions in those not receiving specially packed tablets. This suggests that both groups were equally compliant: the knowledge that the serum digoxin concentration was being monitored may have been the overriding incentive. Where such efforts are not made compliance will be more variable and our prescribing method may apparently underpredict dose requirement.

The prescribing aid, containing these 8 characteristics, gives dosages suitable for patients with normal atrioventricular conduction. Those with impaired conduction, requiring digoxin for the treatment of heart failure, should not be given more than three-quarters of the predicted dose in order to avoid bradycardia (Dobbs *et al.*, 1977b). We hope to identify any other groups requiring special treatment by a multicentre trial of the method in the U.K.

It must be remembered that the work was carried out using a single brand of digoxin tablets with a dissolution rate greater than 90 per cent in 1 hour (Lanoxin, Wellcome Medical Division Ltd., U.K. and Ireland Region). It may be necessary to modify the predicted dose slightly (by multiplying by a constant) when prescribing tablets of another brand in this country or of the same brand manufactured elsewhere.

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Appendix

ADJUSTED R^2

The use of adjusted R^2 has the advantage (Huang, 1970) of making allowance for the number (k) of independent variables in the equation. For a sample of n patients it is given by $1 - (1 - R^2)(n - 1)/(n - k - 1)$.

STATISTICAL ADEQUACY OF FINAL EQUATION

The validity of the F-tests and of the estimated predictive value of the final equation in a future patient depends on the residual error being normally distributed, and therefore of constant variance, and the equation having no systematic lack of fit. These assumptions were tested as follows.

Residual error was plotted against the predicted log dose requirement for each of our 129 patients (Fig. 1). This gave no indication that the model was inadequate (Draper and Smith, 1966; Daniel and Wood, 1971). (A previous trial using dose requirement as the dependent variable in the multiple linear regression analysis had resulted in residual errors which increased with increase in size of the predicted dose, i.e. errors of non-constant variance.)

Examination of the plots of residual error against each of the independent variables did not reveal any evidence of lack of fit (Draper and Smith,

Fig. 1 Residual error versus predicted log dose (129 patients): 125 points are shown, 4 of which each represent 2 patients.

Fig. 2 Cumulative distribution of residual errors. For cumulative frequencies up to 10 per cent and greater than 90 per cent every point is plotted. For frequencies from 10 to 20 per cent, and from 80 to 90 per cent, alternate points are plotted. For the remainder only every fourth point is shown.

1966; Daniel and Wood, 1971) between the final equation and the data.

The cumulative distribution of the residual errors was plotted (Fig. 2). By comparison with the cumulative distribution of a similar number of random normal deviates (Daniel and Wood, 1971) the figure showed no evidence of lack of normality.

ESTIMATION OF RESIDUAL VARIANCE (in units of $\log^2_{10}$ (dose in mg))

The residual variance of the final equation was 1.36×10^{-2} . However, if the equation were to be used in a future patient a slightly larger variance would be expected. The increment stems from uncertainty in the equation coefficients resulting from the finite size of our patient sample. Its magnitude would depend on the values of the independent variables in the future patient. When estimated from the variance-covariance matrix of the equation coefficients (Draper and Smith, 1966), using the combinations of values for independent variables met in our patients, it had a mean of 0.09×10^{-2} and a maximum of 0.25×10^{-2} . Taking the mean value, this gave a total estimated residual variance in a future patient of 1.45×10^{-2} , i.e. $(1.36 + 0.09) \times 10^{-2}$, with the 95 per cent confidence limits (χ^2 distribution, degrees of freedom = 120, i.e. $n - k - 1$) shown in Table 3.

Restricting the doses prescribed by the final equation to practical sizes would cause an additional increase in the residual variance. The doses

recommended in Table 5, step 2, were chosen to correspond to approximately constant increments in log dose, the dose assigned to a patient being that whose log was nearest to the log dose requirement predicted by the equation. This restriction resulted in an increase in the residual variance of the final equation of 0.22×10^{-2} in our patients, and, therefore, an expected residual variance of 1.67×10^{-2} , i.e. $(1.45 + 0.22) \times 10^{-2}$, in a future patient. Similarly use of the simplified method of prescribing (Table 5, steps 1 and 2) resulted in an increase in residual variance of 0.25×10^{-2} in our patients; and, therefore, an expected residual variance of 1.70×10^{-2} , i.e. $(1.45 + 0.25) \times 10^{-2}$, in a future patient.

Using the above estimates of residual variance, the probability of a patient achieving a mean steady state digoxin concentration within the therapeutic range when his maintenance dose was selected according to the criteria in Table 4 could be calculated. (A normal distribution was used for this purpose since it is almost identical to the t-distribution with 120 degrees of freedom.)

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