INFLUENCE OF DIET ON DIGOXIN DOSE REQUIREMENTS

The dose of digoxin required to achieve a chosen concentration cannot be predicted with confidence from renal function. Variability in absorption (Johnson & Bye, 1975) and in biliary excretion (Cauldwell & Cline, 1975) have been suggested as important factors, both of which may be influenced by diet. Food may reduce the absorption of a drug by delaying gastric emptying, by dilution, or by adsorption of the drug to its constituents (Prescott, 1974), whilst its fat content stimulates the excretion of bile. We have attempted to quantify the influence of diet on digoxin dose requirement in general medical outpatients.

Eighty-six digoxin-taking patients consented to take part in the study. They were prescribed 'Lanoxin' tablets to be taken in a single daily maintenance dose at 10.00 h. Efforts to encourage patient compliance, including the use of calendar packs, were made. One month was allowed for steady state conditions to be achieved, after which venous blood samples for digoxin assay (β -Lanoxitest) were taken, just before the daily dose, on an average of five occasions per patient.

The dose of digoxin needed to achieve a pre-dose serum concentration of 1.3 nmol/l (1.0 ng/ml) was calculated using the proportional relationship between daily dose and steady state concentration in an individual, demonstrated in this clinic (Dobbs, Parkes & Rodgers, 1976). The mean value for each patient 'the dose requirement' was used in the following analysis. The group had a mean $\pm$ s.d. dose requirement of 0.30 ± 0.10 mg.

Detailed dietary histories were taken to establish the food and fluid intake on a typical weekday. The accuracy of the information was checked by presenting each patient with the menu described, during a day spent in the medical unit. A computer program was used to analyse the diets. The results are summarized in Table 1.

The daily protein, fat, carbohydrate, energy, fibre and fluid intake had no direct correlation with dose requirement ($P > 0.1$ in each case). Since dose requirements primarily depend on renal function, we attempted to separate the effect on dose of diet from that of renal function using a multiple linear regression

program (Nie, Hull, Jenkins, Steinbrenner & Bent, 1975). The relationship between dose requirement and each dietary constituent, when the effect of blood urea (Halkin, Sheiner, Peck & Melmon, 1975) or creatinine clearance (Dobbs, Mawer, Rodgers, Woodcock & Lucas, 1976) has been allowed for, can be expressed by a partial correlation coefficient.

Table 2 shows protein intake (P g/day) had a highly significant partial correlation with dose requirements (D mg/day), allowing for the effect of blood urea concentration (U mmol/l), the corresponding multiple linear regression equation being:

$$D = (392.5 - 32.5U + 1.7P)10^{-3}$$

However, the protein term in the equation may represent a correction for the effect of protein intake on the urea concentration, rather than an independent effect of diet on dose requirement. Fat intake had a partial correlation with the dose of lower significance (Table 2).

Whereas the above equation explained only 33% of the variance in dose requirement, endogenous creatinine clearance, predicted by entering the patient's serum creatinine concentration, body weight, age, and sex into the nomogram of Siersbaek-Nielsen, Hansen, Kampmann & Kristensen (1971) explained 45%. Table 3 shows the contribution of each variable entered in the nomogram to the prediction of dose requirements. Age was of no additional predictive value to an equation containing weight (W kg), serum creatinine concentration (Cr μ mol/l), and sex (S). Allowing for the effect of these three variables, fat intake (F g/day) was the only dietary constituent with a significant partial correlation with the dose (Table 4). The corresponding equation was:

$$D = (323.7 + 4.0W - 4.3Cr + 54.4S + 0.7F)10^{-3}$$

Table 2 The relationship between digoxin dose requirement, blood urea concentration and daily food intake in 86 outpatients

The table gives the partial correlation of each dietary constituent with dose requirements when the effect of blood urea is removed.

Table 1 Variation in diet in 86 outpatients

Intake/day	Mean	1 s.d.	Range
Protein (g)	62	16	38-118
Fat (g)	76	24	22-157
Carbohydrate (g)	194	61	64-362
Energy (MJ)	7.24	1.8	3.4-12.6
Fibre (g)	2.87	1.23	0.79-7.68
Fluid (l)	1.49	0.59	0.60-4.20

Intake/day	Partial correlation coefficient	P
Protein	0.30	<0.01
Fat	0.27	<0.05
Carbohydrate	0.01	>0.5
Energy	0.18	>0.05
Fibre	0.03	>0.5
Fluid	0.04	>0.5

Table 3 Prediction of dose requirement from serum creatinine concentration, age, sex and body-weight using a multiple linear regression program

The variables were entered into the regression equation in the sequence shown, the order being determined by the potential contribution each variable would make to the explained variance

Step	Variable entered	F* to enter	P	100r ² **
1	Body-weight	17.8	<0.001	17
2	Serum creatinine concentration	28.4	<0.001	38
3	Sex***	9.4	<0.005	45
4	Age	2.9	>0.05	—

* The F value for each variable is derived from the reduction in the residual sum of squares on its entry into the equation.

** Cumulative percent of the variance in dose requirement explained after each step.

*** Score: female = 1; male = 2.

Table 4 Effect of diet on digoxin dose requirements in 86 outpatients

The table gives the partial correlation of each dietary constituent with dose requirement, allowing for the effect of body-weight, serum creatinine concentration and sex

Intake/day	Partial correlation coefficient	P
Protein	0.16	>0.1
Fat	0.22	<0.05
Carbohydrate	-0.02	>0.5
Energy	0.12	>0.1
Fibre	-0.11	>0.1
Fluid	-0.05	>0.5

Substituting in the equation shows that the patient with the highest fat intake (157 g/day) would require approximately 0.1 mg digoxin more than the patient with the lowest intake (22 g/day), assuming other independent variables to be the same.

None of the dietary constituents of the food taken in the 4 h before the dose had either a direct correlation with dose requirement, or a partial correlation when allowance was made for the effects of weight, serum creatinine concentration and sex. This is in agreement with the findings of White, Chamberlain, Howard & Smith (1971) that whether digoxin is taken before or after breakfast has no effect on the steady state concentrations achieved.

Andersson, Nyberg, Dencker & Göthlin (1975) have demonstrated that 50% of the digoxin from an aqueous solution had been absorbed into the portal vein after 2 hours. After 6 h the maximal absorption attainable from aqueous solution (Johnson & Bye, 1975), a mean of 64%, had been achieved. By gastro-intestinal aspiration after oral dosing, Beerman, Hellström & Rosén (1972) have demonstrated gastric absorption, as well as considerable absorption in the

proximal part of the small intestine. Digoxin can be absorbed from the colon under experimental conditions (Andersson *et al.*, 1975; Ochs, Bodem, Schäfer, Kodrat & Dengler, 1975), but this is unlikely to be of clinical relevance. In view of the initial rapid absorption, one would expect that, if fat reduced absorption, the content of the patients' breakfasts would have been at least as important as the daily intake. This was not the case.

Sumner, Russell & Whiting (1976) found that approximately 30% of the elimination of an intravenous digoxin dose is extra-renal in healthy volunteers. This is supported by Cauldwell & Cline's (1975) estimate of biliary excretion. Administration of cholecystokinin via an intestinal tube can cause an increase in biliary excretion of digoxin, when given from zero to 24 h after an oral dose of digoxin (Beermann *et al.*, 1972). A high fat intake may have a similar effect.

Our study suggests that the dietary fat content is one of the variables determining the rate of elimination of digoxin. Sheiner, Rosenberg, Marathe & Peck, 1973, found that serum digoxin concentrations achieved by outpatients averaged only 72% of those expected from a model based on the dose given to inpatients and their body size and renal function. This may reflect the low fat intake of ill patients, as well as the non-compliance of outpatients.

Warning. The equations given apply only to outpatients with serum creatinine concentrations of less than 140 µmol/l.

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References

- ANDERSSON, K.E., NYBERG, L., DENCKER, H. & GÖTHLIN, J. (1975). Absorption of digoxin in man after oral and intrasigmoid administration studied by portal vein catheterization. *Eur. J. clin. Pharmac.*, **9**, 39–47.
- BEERMANN, B., HELLSTRÖM, K. & ROSÉN, A. (1972). The absorption of orally administered (12α - ^3H) digoxin in man. *Clin. Sci.*, **43**, 507–518.
- CAULDWELL, J.H. & CLINE, T. (1975). Biliary excretion of digoxin in man. *Clin. Pharmac. Ther.*, **19**, 410–415.
- DOBBS, S.M., MAWER, G.E., RODGERS, E.M., WOODCOCK, B.G. & LUCAS, S.B. (1976). Can digoxin dose be predicted? *Br. J. clin. Pharmac.*, **3**, 231–237.
- DOBBS, S.M., PARKES, J. & RODGERS, E.M. (1976). Digoxin: Linearity between dose and serum concentration. *Br. J. clin. Pharmac.*, **3**, 940–941.
- HALKIN, H., SHEINER, L.B., PECK, C.C. & MELMON, K.L. (1975). Determinants of the renal clearance of digoxin. *Clin. Pharmac., Ther.*, **17**, 385–394.
- 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.
- NIE, N.H., HULL, C.H., JENKINS, J.G., STEINBRENNER, K. & BENT, D.H. (1975). *Statistical package for the social sciences*, 2nd Ed., pp. 320–367. New York: McGraw-Hill.
- OCHS, H., BODEM, G., SCHÄFER, P.K., KODRAT, G. & DENGLER, H.J. (1975). Absorption of digoxin from the distal parts of the intestine in man. *Eur. J. clin. Pharmac.*, **9**, 95–97.
- PRESCOTT, L.F. (1974). Gastrointestinal absorption of drugs. *Med. Clin. N. Am.*, **58**, 907–916.
- SCHEINER, 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-NEILSEN, K., HANSEN, J.M., KAMPMANN, U. & KRISTENSEN, M. (1971). Rapid evaluation of creatinine clearance. *Lancet*, **i**, 1133–1134.
- SUMNER, D.J., RUSSELL, A.J. & WHITING, B. (1976). Digoxin pharmacokinetics: multicompartmental analysis and its clinical implications. *Br. J. clin. Pharmac.*, **3**, 221–229.
- WHITE, R.J., CHAMBERLAIN, D.A., HOWARD, H. & SMITH, T.W. (1971). Plasma concentrations of digoxin after oral administration in the fasting and post-prandial state. *Br. med. J.*, **1**, 380–381.

EFFECT OF AEROSOL IPRATROPIUM BROMIDE (SCH 1000) ON SPUTUM VISCOSITY AND VOLUME IN CHRONIC BRONCHITIS

In chronic bronchitis anticholinergic drugs are more likely to produce bronchodilation than β -adrenoreceptor stimulant drugs (Poppius & Salorinne, 1973). These drugs have not found an established place in clinical practice because atropine may inhibit secretion of the bronchial glands, leading to drying of the bronchial mucous membrane (Goodman & Gilman, 1970). This may lead to an increase in the viscosity of the bronchial secretion and to an increase in airways obstruction. We report here the effect of a new anticholinergic drug which is similar to atropine, ipratropium bromide (Boehringer Ingelheim), on

sputum volume and viscosity when given by aerosol to bronchitic subjects in a controlled trial.

Twelve bronchitic in-patients were studied. They were all producing mucoid sputum and were given two puffs of ipratropium bromide (40 μg) or two puffs of an identical placebo aerosol containing propellant only, for 2 days, the order of the treatments being randomized. All sputum was collected and its volume measured for 24 h and sputum production from mid-day to 15.00 h was collected separately and the apparent viscosity measured at a shear rate of 700 s^{-1} with a Ferranti-Shirley cone and plate viscometer