DIGOXIN: LINEARITY BETWEEN DOSE AND SERUM CONCENTRATION

A study of variables relevant to digoxin dosage (Dobbs, Mawer, Rodgers, Woodcock & Lucas, 1976) was based on the assumption that the serum digoxin concentration achieved was directly proportional to the daily dose given in each patient. Wagner, Northam, Alway & Carpenter (1965), list several phenomena which invalidate this assumption for a given drug. The most likely of these to be relevant to digoxin is variation in the fraction of the drug absorbed (Johnson & Bye, 1975). Redfors (1972), was able to demonstrate a linear relationship between size of daily digoxin dose and the serum concentration achieved just before a dose in a small group of patients. The following studies test this assumption with respect to 1) loading doses given to normal subjects and 2) maintenance therapy in consecutive out-patients requiring alteration of their digoxin maintenance dose.

The digoxin tablets used were Lanoxin brand (Wellcome Medical Division). Blood samples were assayed using a β Lanoxitest kit (Wellcome Reagents Ltd). The between assay coefficient of variation of a serum sample assayed in duplicate

Figure 1 Comparison of the mean concentration achieved in the 24 h following loading doses of 0.5, 0.75 and 1.0 mg in five volunteers.

Figure 2 The calendar packs

was 10% at concentrations of 1.3 nmol/l and of 2.6 nmol/l ($n = 20$ in each case).

Five healthy adults (three male, two female) gave informed consent. Ages ranged from 28 to 40 years and weight from 58 to 75 kg; creatinine clearances were greater than 90 ml/min. Each subject received oral loading doses of 0.5, 0.75 and 1.0 mg in random order. The loading dose was taken at 10.00 h on each occasion, the subjects having eaten their normal breakfast at the usual time. A fortnight was allowed between doses. Venous blood samples for digoxin assay were collected immediately before each dose, and at 0.5, 1, 1.5, 2, 4, 6, 8, and 24 h after the dose. The mean concentration achieved in the 24 h following the dose was derived from the area under the concentration/time curve (calculated using the trapezoidal rule). Figure 1 shows a linear relationship between size of loading dose and the mean serum concentration achieved ($r = 0.86$, $P < 0.001$).

The serum digoxin concentrations of eighty-seven out-patients who required alteration in maintenance dose were studied. Doses were adjusted by a factor ranging from a quarter to twice the original dose. Ages ranged from 45 to 77 years, weight 38 to 78 kg and creatinine clearance 38 to 139 ml/min (mean $\pm$ s.d., 65.4 ± 18.7 ml/min). The serum creatinine concentration was stable in each case. The digoxin tablets were dispensed in calendar packs (Figure 2) to encourage patient compliance. The daily dose was taken at 10.00 h. At each clinic visit remaining digoxin tablets were collected and a new supply issued. After a minimum of 3 weeks on each maintenance dose regime a venous blood sample for digoxin assay was taken immediately before

Figure 3 Comparison of the serum concentration predicted following a dosage change with that measured by radioimmunoassay in eighty-seven out-patients. The regression line and its 95% confidence limits are shown.

the daily dose. Patients adhered to their normal dietary pattern throughout the study.

If a linear relationship exists between size of maintenance dose and the serum concentration achieved, then the predicted concentration, P nmol/l, achieved by a dose D_2 mg will be given by $P = C_1 D_2 / D_1$, where C_1 nmol/l is the serum concentration that was achieved when the original dose D_1 mg was given. This prediction is compared with the measured concentration achieved by dose D_2 mg in Figure 3.

Tablet counting revealed that two patients (F.A. & A.B.) did not take the original maintenance dose as prescribed. Another two patients (A.W. & A.L.) admitted retrospectively, to non-compliance with one dose regime. Excluding these four patients, a highly significant correlation between predicted and measured concentration was found for the remaining eighty-three dose changes ($r = 0.86$, $P < 0.001$). The slope of the regression line (0.91 ± 0.06 , 1 s.e. mean) did not differ significantly from 1, and the origin lay within the 95% confidence limits of the line.

It was concluded that the assumption of linearity between dose given and serum concentration achieved by a subject was justified in both normal subjects receiving loading doses and out-patients taking maintenance therapy. Non-compliance should be suspected if the expected change in serum concentration does not result from a dose adjustment in a patient with stable renal function.

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References

- DOBBS, S.M., MAWER, G.E., RODGERS, E.M., WOODCOCK, B.G. & LUCAS, S.B. (1976). Can digoxin dose requirements be predicted? *Br. J. clin. Pharmac.*, **3**, 231-237.
- JOHNSON, B.F. & BYE, C. (1975). Maximal intestinal absorption of digoxin and its relationship to steady state plasma concentration. *Br. Heart J.* **37**, 203-208.
- REDFORS, A. (1972). Plasma digoxin concentration—its relation to digoxin dosage and clinical effects in patients with atrial fibrillation. *Br. Heart J.*, **34**, 381-391.
- WAGNER, J.G., NORTHAM, J.I., ALWAY, C.D. & CARPENTER, O.S. (1965). Blood levels of drug at equilibrium state after multiple dosing. *Nature, Lond.*, **207**, 1301-1302.