Table 1 Mean $\pm$ s.e. mean salivary digoxin levels at each dosage of digoxin

Subject	Mean salivary digoxin (ng/ml)			
	Digoxin (0.125 mg/day)	Digoxin (0.25 mg/day)	Digoxin (0.50 mg/day)	Digoxin (0.625 mg/day)
A (δ , 65 kg)	0.37 $\pm$ 0.06	0.54 $\pm$ 0.05	0.93 $\pm$ 0.15	—
B (δ , 74 kg)	—	0.36 $\pm$ 0.08	0.81 $\pm$ 0.08	1.28 $\pm$ 0.3
C (φ , 57 kg)	0.27 $\pm$ 0.04	0.7 $\pm$ 0.15	0.83 $\pm$ 0.15	1.56 $\pm$ 0.19
D (φ , 54 kg)	0.52 $\pm$ 0.14	1.2 $\pm$ 0.09	1.18 $\pm$ 0.12	—

of his fingers. On two occasions subjects inadvertently collected saliva after taking their tablets and showed salivary levels in excess of 4 ng/ml.

Figure 1 shows salivary digoxin concentrations plotted against serum levels. The slopes of the linear regression equations were 1.3, 0.74, 0.72 and 0.54 for A, B, C and D respectively.

From these results it appears that a statistically significant linear correlation exists between serum and salivary digoxin levels done without prior ethanol extraction and that the latter shows a progressive increase with increasing dosage.

As saliva is an easily accessible body fluid and can, for instance, be collected at home by patients, it appears to be a promising medium for monitoring digoxin therapy, especially when serial information is needed.

Some problems have been highlighted by the study and it must be kept in mind that contamination can occur and that tablets should not be handled before collecting saliva and that collection should be done just prior to oral administration of the next digoxin dosage.

As indicated by the differences in the slopes of the linear regression equations there appears to be

a certain degree of individual variation, which tends to indicate that serial estimations could be of more value than would single estimations.

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References

- GLYNN, J.P. & BASTAIN, W. (1973). Salivary excretion of paracetamol in man. *J. Pharm. Pharmac.*, **25**, 420-421.
- GRAHAM, G. & ROWLAND, M. (1972). Application of salivary data to biopharmaceutical studies of salicylates. *J. pharm. Sci.*, **62**, 1219-1222.
- HUFFMAN, D.H. (1975). Relationship between digoxin concentration in serum and saliva. *Clin. Pharmac. Ther.*, **17**, 310-312.
- KOYSOOKO, R., ELLIS, E.F. & LEVY, G. (1974). Relationship between theophylline concentration in plasma and saliva of man. *Clin. Pharmac. Ther.*, **15**, 454-460.

SERUM DIGOXIN CONCENTRATIONS

Since radioimmunoassay of digoxin is an expensive, time consuming procedure, a guide to the optimal timing of samples is needed. Review of the literature shows a lack of standardisation of sampling time (Chamberlain, White, Howard & Smith, 1970; Jelliffe & Brookes, 1974; Wagner, Yates, Willis, Sakmar & Stoll, 1974; Carruthers, Kelly & McDevitt, 1974; Curtis, 1975). This makes studies difficult to compare, and exaggerates the

overlap between toxic and therapeutic concentrations.

Response to digoxin administration has been shown to depend on the concentration attained in the tissue compartment (Shapiro, Narahara & Taubert, 1970; Schoenwald, 1974). In practice the best available guide to mean tissue concentration achieved during maintenance therapy is the mean steady state serum concentration (Dobbs, Mawer,

Rodgers, Woodcock & Lucas, 1976). Usually a single serum sample must suffice as an estimate of this.

The relationship between the mean steady state serum concentration and the serum concentration at each of five sampling times was studied. The data were obtained from forty-five consecutive out-patients receiving digoxin (Lanoxin) tablets in a general medical clinic (aged 45-77 years, weight 38-77 kg, creatinine clearance 38-139 ml/min). Venous blood samples were collected just before, and at 1, 2, 4 and 7 h after the daily maintenance dose in each subject. The samples were assayed in duplicate using a Lanoxitest β kit (Wellcome Reagents Ltd), the coefficient of variation of the assay being 8% at a concentration of 2.4 nmol/l and 11% at 1.0 nmol/l. The mean serum concentration was calculated for each patient from the area under the concentration time curve during a dose interval using the trapezoidal method. (Johnson & Bye, 1975).

Table 1 shows the correlation between the assayed concentration at each of the five sampling times and the calculated mean serum concentration in the forty-five patients. The constants for the corresponding regression equations are given.

The ability to predict the mean concentration from a single assay result is maximal 7 h after the dose ($100r^2 = 96\%$). At this time the concentration assayed approximately equals the mean concentration ($\bar{C} = 0.05 + 0.93.C_t$). Samples taken in the first 2 h after a dose give only a broad guide to the mean concentration ($100r^2 = 76\%$ or less), but at 4 h and after accurate predictions can be made. Routine inclusion of such estimates in assay reports would make reference to the therapeutic range more meaningful. For example a serum digoxin

concentration of 2.2 nmol/l just before a daily dose (mean concentration = 2.7 nmol/l, i.e. $0.37 + 1.08.C_t$) would carry a higher risk of toxicity than the same assay result obtained for a sample taken 4 h after a dose (mean concentration = 1.9 nmol/l, i.e. $0.22 + 0.76.C_t$).

When the administration of the daily dose is divided, and where renal failure is present, the steady state concentration time curve is relatively flat, and corrections for sampling time less important.

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References

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.

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Table 1 Calculation of mean steady state serum digoxin concentration

The mean steady state concentration, $\bar{C}$ (nmol/l), is given by:-

$$\bar{C} = a + b.C_t$$

where C_t (nmol/l) is the assayed serum concentration at t hours after the maintenance dose, and a and b are constants for that sampling time

sampling time t (h)	a (nmol/l)	b	correlation coefficient (r^2)	coefficient of determination $100r^2$ (%)
0 (pre-dose)	0.37	1.08	0.95	90
1	0.69	0.38	0.72	52
2	0.24	0.56	0.87	76
4	0.22	0.76	0.94	89
7	0.05	0.93	0.98	96

* $P < 0.001$ in each case

Conversion: SI to traditional units 1 nmol/l $\approx$ 0.78 ng/ml

- 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.
- CURTIS, P. (1975). Long term digoxin treatment in general practice. *Br. med. J.*, **4**, 747-750.
- 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.
- JELLIFFE, R.W. & BROOKES, G. (1974). A nomogram for digoxin therapy. *Am. J. Med.*, **57**, 63-68.
- 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.
- SHAPIRO, W., NARAHARA, K. & TAUBERT, K. (1970). Relationship of plasma digitoxin and digoxin to cardiac response following intravenous digitalisation in man. *Circulation*, **42**, 1065-1072.
- SCHOENWALD, R.D. (1974). Evidence for variable digoxin absorption as estimated by pharmacological response activities. *J. pharm. Sci.*, **63**, 411-416.
- 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.