VARIATIONS OF PLASMA DIGOXIN CONCENTRATIONS IN THE EQUILIBRIUM STATE AFTER MULTIPLE DOSING

The measurement of plasma digoxin concentrations by radioimmunoassay has provided a valuable tool in recent years for research into the clinical pharmacology of digoxin and also as a measure of therapeutic activity in clinical practice (Chamberlain, 1973). In the latter area, the scope includes aid to determining optimal doses in malabsorption syndromes and renal failure, in the diagnosis of toxicity, and as a guide to the treatment of refractory fast atrial fibrillation. Recently plasma digoxin concentration estimations have been used to evaluate drug compliance by measuring digoxin levels in a group of patients on admission to hospital, comparing them with the levels achieved after 7 days treatment with digoxin at the dose level prescribed before admission (Johnston, Kelly & McDevitt, 1977). It was assumed that equilibrium would have been attained within that period and that alterations in plasma digoxin concentrations indicated poor compliance, provided renal function had not changed. On the basis of reproducibility of the laboratory methods, changes in plasma digoxin concentrations of greater than 0.2 ng/ml (conversion factor 1.0 ng/ml $\equiv$ 1.3 nmol/l) and in serum creatinine of greater than 17.6 μ mol/l within individual patients were considered to represent real changes in plasma levels and in renal functions respectively. Whiting, Sumner & Goldberg (1973) have previously reported that laboratory variation in the technique of estimating plasma digoxin by radioimmunoassay accounts for only 10% of a particular reading.

We were concerned that these definitions of compliance based on plasma digoxin concentrations were arbitrary and might result in wrong conclusions, as no information was available about natural fluctuations in concentrations at equilibrium, assuming that compliance was 100%. We have, therefore, investigated plasma digoxin concentrations at steady state after multiple dosing.

Six normal males (aged 27–39 years) volunteered for the study after detailed explanation of what was involved. All had normal renal and hepatic function and were taking no other drugs. On the basis of their age, weight and serum creatinine levels, a daily digoxin dosage was calculated for each individual from a digoxin nomogram (Mawer *et al.*, unpublished observations). Daily digoxin dosage ranged from 0.375 to 0.5 mg and 'Lanoxin' tablets (Burroughs Wellcome) were given to each subject from a central batch. Each subject took his calculated digoxin dose every morning at approximately the same time for a period of 28 consecutive days. Assuming an elimination half-life of 1.6 days for digoxin (Jelliffe, 1968), each subject was allowed 10 days digoxin therapy to achieve equilibrium state. Thereafter 10 ml samples of blood were obtained by direct venipuncture for estimation of plasma digoxin concentration and serum creatinine exactly 6 h after the digoxin dose had been taken on days 11, 13, 15, 18, and 28 of the study (or days 1, 3, 5, 8, and 18 of steady-state, assuming it had been achieved on day 11). Plasma digoxin levels were measured by radioimmunoassay using a modified Wellcome B Lanoxitest Kit method (Ojala, Karjalainen & Reissell, 1972) and the serum creatinine measurements were made in the routine hospital laboratory.

In addition, twenty separate estimations of the plasma digoxin concentration of two single samples were made. These samples were chosen so that one was in the lower concentration range (<0.8 ng/ml) and the other in the usual therapeutic range (0.8–2.0 ng/ml).

The results of the plasma digoxin concentrations obtained in the 6 subjects on five occasions during an 18 day period at equilibrium state are shown in Table 1. The mean plasma levels ranged from 0.96–2.1 ng/ml. In five of the subjects, the maximum variation within the five samples was 0.2 ng/ml: in the

Table 1 Plasma digoxin concentrations (ng/ml) in six subjects in the equilibrium state after multiple dosing

Subject	Day of equilibrium state					Mean	s.d.	Coefficient of variation (%)
	1	3	5	8	18			
1	1.3	1.2	1.4	1.4	1.4	1.34	0.09	6.7
2	2.0	2.0	2.2	2.2	2.2	2.10	0.10	4.8
3	1.9	1.8	1.8	1.9	2.1	1.90	0.12	6.4
4	1.0	1.1	0.9	0.9	0.9	0.96	0.09	9.3
5	1.4	1.6	1.5	—*	1.6	1.52	0.09	6.3
6	1.2	1.0	1.2	1.1	1.2	1.14	0.09	7.8

* Sample not obtained.

Table 2 Serum creatinine levels ($\mu\text{mol/l}$) in six subjects during chronic digoxin administration

Subject	Day of equilibrium state					Mean	s.d.	Coefficient of variation (%)
	1	3	5	8	18			
1	100	100	80	110	95	97	10.9	11.2
2	85	85	100	85	90	89	6.5	7.3
3	105	100	105	100	100	102	2.7	2.6
4	90	110	105	105	100	102	7.5	7.4
5	95	90	105	95	90	95	6.1	6.4
6	100	105	90	80	100	95	10.0	10.5

Table 3 Results of analysing single samples on twenty separate occasions for plasma digoxin concentration (ng/ml)

	Sample 1	Sample 2
Range	0.7–1.0	1.6–2.0
Mean	0.74	1.75
s.d.	0.08	0.11
Coefficient of variation (%)	11.00	6.30

sixth it was 0.3 ng/ml. This gave a coefficient of variation in each subject ranging from 4.8 to 9.3%. Analysis of variance gave 95% confidence limits of ± 0.2 ng/ml.

The corresponding figures for serum creatinine values throughout the study appear in Table 2. All values obtained were within normal limits. The maximum fluctuation within a subject was 30 $\mu\text{mol/l}$, and the coefficient of variation in him was 11.2%. In other subjects it ranged from 2.6 to 10.5%. This gave 95% confidence limits by analysis of variance of ± 16.1 $\mu\text{mol/l}$.

The repeated measurement of digoxin concentrations in single samples (Table 3) showed coefficients of variation of 11.0% for the lower concentration and 6.3% for the normal concentration range.

The coefficients of variation for the radioimmunoassay technique are not dissimilar from those obtained in the study of equilibrium state, suggesting that most of the small variations in plasma concentrations may have been due to laboratory measurement rather than natural fluctuation.

The conclusions of this study, based on a relatively small sample, are that alterations in plasma digoxin levels of greater than 0.4 ng/ml represent real changes in drug concentration and that alterations in serum creatinine of greater than 32.2 $\mu\text{mol/l}$ indicate changes in renal function.

The limits are larger than those previously selected, both in relation to plasma digoxin and serum creatinine (Johnston *et al.*, 1977). Reanalysis of compliance in the original admission study (Johnston *et al.*, 1977) using these new limits shows that of the 50 patients studied 17 (34%), instead of 18 previously, would be adjudged to have been taking less and 5 (10%), instead of 7 previously, more than the prescribed daily digoxin dose before admission to hospital. Overall these new standards would mean 44 (rather than 50) per cent were taking their digoxin improperly. This is a small clinically insignificant difference and does not affect the general conclusions about drug compliance.

We are grateful to Mr T.H. Hassard, M.Sc., for help with the statistical analysis.

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Received July 19, 1977

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