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ESTIMATES OF DIGOXIN BIOAVAILABILITY FROM SHORT-TERM PLASMA PROFILES AND CUMULATIVE URINARY EXCRETION

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SUMMARY

The estimates of relative bioavailability of digoxin tablets by short-term plasma concentration/time curves and cumulative urinary excretion vary almost 2-fold. Short-term plasma concentration/time data tend to overestimate differences in bioavailability of digoxin. The evidence presented suggests that urinary estimates are preferable.

INTRODUCTION

Fraser et al. (1973) described a dissolution test for digoxin tablets which gave an excellent correlation with bioavailability as estimated by measurement of the area under the plasma concentration/time curve from 0 to 6 h. The estimates of bioavailability obtained from such a short period, approximately one-fifth of the half-life, have been criticized on the grounds that absorption of slowly dissolving formulations may be continuing well after the sampling period (Sorby and Tozer, 1973; Beveridge et al., 1973). Similarly, the area under the curve for tablets rapidly releasing digoxin would give early peaks of high altitude and would tend to overestimate their bioavailability.

This paper reports a repeat study on the same four batches of the brands previously studied, using cumulative urinary excretion as the measurement of bioavailability. The results of the two methods of estimating bioavailability are compared.

METHOD

After overnight fasting, healthy subjects showing normal profiles in a battery of 13 routine biochemical investigations followed a strict protocol, and took 0.5 mg digoxin as

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tablets in a cross-over design with each of four brands. No food was permitted for 4 h after ingestion. Complete 24-h urinary collections were made, for 2 days by 6 volunteers and for 7 days by 4 volunteers. After mixing, urine samples were stored at −20°C prior to radioimmunoassay using a method based on the Immophase Kit (Corning Limited, Halstead, Essex). Urines were diluted immediately prior to the assay to bring the concentration within the range recommended and then treated as for the serum method; most specimens required dilution within the range 1 in 5 to 1 in 50. Non-specific urine interference was shown to be absent under these conditions, and was found to be slight at 1 in 2 dilution. Protein error using the standards supplied was found to be minimal. Standard deviations for quality control sera were 0.10 and 0.18 μg/litre at mean digoxin concentrations of 1.44 and 3.00 μg/litre, respectively, analyzed in parallel with the experimental urines throughout the study (n = 12 for each).

RESULTS AND DISCUSSION

Bioavailability was estimated from the cumulative urinary excretion of digoxin at 1, 2, 3 and 7 days after ingestion. The coefficients of variation for urinary recovery after ingestion of 0.5 mg digoxin in 6 subjects varied from 13.4 to 23.9% after 1 day and from 15.6 to 20.4% after 2 days. These figures compared with coefficients of variation of 35.2 to 50.6% in area under the plasma concentration/time curve in 6 subjects in a previous study (Fraser et al., 1973). Full results for the 2-day period are shown in Table 1. As in the previous study tablets of 'Old' Lanoxin (produced between 1969 and May 1972) were arbitrarily selected as a standard by which the bioavailability of the other formulations

TABLE 1

2-DAY CUMULATIVE URINARY EXCRETION OF DIGOXIN IN μg AND BIOAVAILABILITY RELATIVE TO 'OLD' LANOXIN

Subjects	Manufacturer 1 ('New' Lanoxin) 0.5 mg	Manufacturer 3 0.5 mg	Manufacturer 6		Manufacturer 8 ('Old' Lanoxin) 0.5 mg
			0.5 mg	1.0 mg	
1	123.8	93.8	57.1	91.7	71.1
2	106.6	90.2	55.7	121.6	56.8
3	129.9	102.4	62.5	118.0	57.6
4	73.2	78.0	47.8	103.7	69.0
5	88.7	64.0	42.9	63.7	49.3
6	102.2	89.8	42.5	98.7	49.9
Mean	104.1	86.4	51.4	99.6	59.0
S.D.	21.2	13.5	8.23	20.9	9.3
C.V. %	20.4	15.6	16.0	21.0	15.7
Bioavailability (relative to 'Old' Lanoxin)	1.76	1.46	0.87	1.69	1.0

could be compared. Application of the '*t*'-test to this data showed that the bioavailability values of all tablets were significantly different ($P < 0.05$) from each other except the comparison of 'Old' Lanoxin with that from manufacturer 6, and 'New' Lanoxin with that from manufacturer 3.

The relative bioavailability calculated after various periods of urinary collection are shown in Table 2, above the results obtained from measurements of area under the plasma concentration/time curve from 0 to 6 h in the previous study. While the figures for bioavailability at the several urinary collection periods correlate fairly well with each other, they are clearly at variance with those obtained from the area under the curve data. Taking account of the longer time up to 5 half-lives over which the urinary estimates were based, and of the reduced coefficients of variation, the bioavailability figures from urinary data would seem preferable. Further, the bioavailability figures from urinary estimates closely parallel the overall 70% increase in steady state plasma concentration in 19 patients transferred from 'Old' to 'New' Lanoxin reported by Shaw et al. (1974). Such findings contrast sharply with the 3-fold variation in steady-state levels predicted between 'Old' and 'New' Lanoxin using the short-term plasma studies. Beveridge et al. (1975) have also reported a 2-fold difference in bioavailability of digoxin when estimated by areas under the plasma concentration/time curve and urinary excretion methods.

Huffman et al. (1974) reported that doubling the dose of ingested digoxin failed to double the area under the plasma concentration/time curve from 0 to 24 h, but correctly doubled the 24-h urinary excretion. Our data derived from columns 4 and 5 of Table 1 show that 1.94 times the single dose was excreted when the dose was doubled. The similar figure after 24 h was 1.96. Such findings add further preference for urinary

TABLE 2

COMPARISON OF RELATIVE BIOAVAILABILITY OF 4 BRANDS OF DIGOXIN TABLET USING URINARY EXCRETION AND AREA UNDER THE CURVE DATA

Time in days	Relative bioavailability, as: Mean cumulative urinary excretion after 0.5 mg of other brands / Mean cumulative urinary excretion after 0.5 mg of 'Old' Lanoxin			
	Manufacturer 1 'New' Lanoxin	Manufacturer 3	Manufacturer 6	Manufacturer 8 'Old' Lanoxin
1	1.71	1.43	0.82	1.0
2	1.76	1.46	0.87	1.0
3 [a]	1.63	1.37	0.87	1.0
7 [a]	1.45	1.33	0.86	1.0
	Relative bioavailability, as: Mean area under 0–6 h serum concentration/time curve for other brands / Mean area under 0–6 h serum concentration/time curve for 'Old' Lanoxin			
	2.93	1.94	0.90	1.0

[a] 4 Volunteers only.

TABLE 3

CORRELATION BETWEEN AMOUNT OF DIGOXIN IN SOLUTION AND BIOAVAILABILITY ESTIMATED FROM CUMULATIVE URINARY EXCRETION DATA

Dissolution time (h)	Correlation coefficient			
	1 day	2 day	3 days [a]	7 days [a]
0.5	0.86	0.88	0.88	0.81
1	0.96	0.97	0.97	0.93
2	0.93	0.94	0.93	0.96
3	0.93	0.94	0.93	0.94

[a] 4 Volunteers only

excretion, rather than short-term plasma concentration data for estimating digoxin bioavailability.

Previous studies have shown excellent co relation between the in vitro dissolution test and in vivo findings, and it seemed important, therefore, to re-investigate this relationship with the estimates of bioavailability reported above. A re-determination of digoxin in solution at various time intervals in the dissolution process prior to the repeat bioavailability study using urinary recoveries, gave identical results to those obtained 18 months previously, for the 3 brands for which samples remained. The results of correlation between the weights dissolved, and the bioavailability estimates are shown in Table 3. A good correlation obtains again between bioavailability and the amount of digoxin in solution at 1 h in the dissolution test. However, the coefficient 0.97 is less satisfactory than the 0.995 value derived previously from the plasma data.

In conclusion, it appears that short-term plasma studies necessitated by the relative insensitivity of radioimmunoassays, tend to overemphasise differences in bioavailability of digoxin. Results derived from cumulative urinary excretion studies are preferred since higher concentrations of drug appear in urine, aiding analysis; individual differences estimated by coefficients of variation are reduced; samples can be collected over several half-lives (although 24-h would appear sufficient); and the results obtained more accurately reflect the steady-state concentrations found in clinical practice.

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