A completely absorbed oral preparation of digoxin

Digoxin absorption was studied in healthy volunteers by determination of peak plasma concentrations, areas under plasma concentration curves, and urinary excretion after single-dose administration. By comparison with an aqueous solution, increased rate and extent of absorption occurred from experimental soft gelatin formulations of digoxin in solution. Enhanced bioavailability of the capsules was not affected by altered volume of contained solvent. Digoxin was considerably better absorbed from capsules than from tablets of moderately high dissolution rate. Mean percentage intestinal absorption was 75% from tablet and 97% from capsules. Reduced between-subject variability accompanied the enhanced absorption from capsules.

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It has been established that the bioavailability of digoxin is related to its rate of dissolution from tablets,[5] suggesting that digoxin must dissolve in aqueous intestinal fluids before it can be absorbed. Theoretically, an aqueous digoxin solution should have maximal bioavailability, but it has been reported in an abstract[9] that bioavailability is greater from soft gelatin capsules containing digoxin in a solution of polyethylene glycol than from tablets of high dissolution rate. This was a surprising finding as such tablets did not significantly differ from aqueous solution in other studies.[6] The possibility that soft gelatin encapsulation might have unexpected beneficial effects on digoxin absorption was examined by comparing an aqueous solution with two capsules of differing volume of solvent but equal digoxin content. It was decided also to compare absorption of digoxin from soft gelatin capsules and from a suitable reference tablet. The selected digoxin tablets were those that are most widely prescribed in the United States.

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Methods

First experiment.

Treatments. The treatments administered were: (1) 0.4 mg of U.S.P. digoxin dissolved in 200 ml of water with 3 ml of ethanol. (2) Two standard 0.25-mg digoxin (Lanoxin) tablets manufactured in the United States (batch 960-K), and with a dissolution rate of 77% in 1 hr. (3) Two experimental soft gelatin capsules each with a final volume size of 7.5 minims (0.47 ml), and each containing 0.2 mg digoxin dissolved in solvent, which consisted of 90% polyethylene glycol 400, 6% ethanol, 3% propylene glycol, and 1% water. (4) Two experimental soft gelatin capsules (Lanoxicaps)

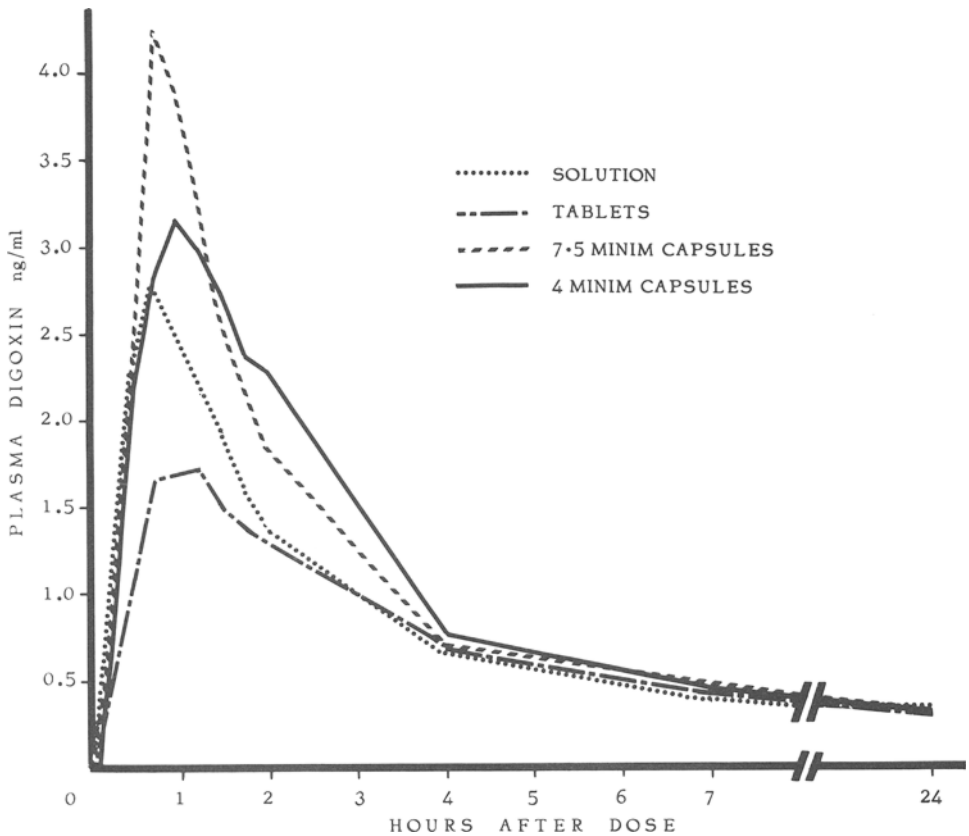

Fig. 1. Comparison of mean plasma concentration curves after 0.5 mg of digoxin administered as tablets, or after 0.4 mg administered as a solution or as capsules.

each with a final volume size of 4 minims (0.25 ml) and each containing 0.2 mg digoxin in the preceding solvent.

Procedure. The subjects were 8 healthy volunteers; because 1 failed to complete all treatment occasions, only results from 7 are reported. Three subjects were male and 4 female; ages ranged from 19 to 43 and body weight from 51 to 115 kg. None had a past history of serious illness, and none was taking medications other than oral contraceptives. Subjects received single doses of each treatment, the sequence of occasions being randomized by a Latin-square design, and at least 14 days separated occasions. Treatments were administered at 9.0 A.M. after an overnight fast. Tap water, 200 ml, was swallowed in conjunction with treatments 2, 3, and 4, and nothing else was allowed by mouth for a further 3 hr. Blood samples were obtained via a Braunula cannula in an arm vein at 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2, 4, 7, and 24 hr, and urine was collected in 24-hr periods for 6 days after ingestion of each treatment. Completeness of urinary collection was assessed by determination of urinary creatinine excretion.

Second experiment.

Treatments. The treatments administered were: (1) 0.5 mg of digoxin as 2 ml of digoxin injection fluid mixed with 100 ml of 5% dextrose solution immediately before intravenous administration over a period of 45 min. (2) 0.5 mg of digoxin (USA batch 960-K). (3) 0.4 mg of digoxin as 2 experimental soft gelatin capsules (Lanoxicaps) each of 4 minims (0.25 ml) final volume.

Procedure. The subjects were 12 healthy volunteers; 9 were male and 3 female, ranging in age from 19 to 59 and in body weight from 49 to 88 kg. None had a past history of serious

Table I. *Peak plasma digoxin concentrations (ng/ml)*

Subject	*0.4 mg in water*	*0.5 mg in tablets*	*0.4 mg in capsules (7.5 minim)*	*0.4 mg in capsules (4 minim)*
S.	2.8	1.9	4.9	5.3
P.	2.5	2.6	3.7	3.6
M.	2.8	1.6	4.7	3.7
C.	2.9	2.1	3.8	4.4
B.	2.9	1.4	5.2	3.5
A.	2.4	2.0	4.0	3.9
W.	3.9	2.8	4.7	3.4
Mean	2.91	2.07	4.42	3.97
SEM	0.18	0.19	0.22	0.25

Table II. *Area under plasma concentration curve over 24 hr ($ng \cdot ml^{-1}hr$)**

Subject	*0.4 mg in water*	*0.5 mg in tablets*	*0.4 mg in capsules (7.5 minim)*	*0.4 mg in capsules (4 minim)*
S.	14.8	13.9	18.3	20.2
P.	15.5	16.7	19.0	17.4
M.	13.1	14.4	16.9	17.2
C.	15.0	10.1	16.1	16.0
B.	9.0	7.2	12.2	13.7
A.	14.0	10.6	15.5	14.9
W.	14.4	15.3	16.9	15.4
Mean	13.7	12.6	16.4	16.4
SEM	0.8	1.3	0.8	0.8
CV	16.1	26.8	13.5	13.0

*Range of values with each treatment is indicated by standard error of the mean (SEM) and coefficient of variation (CV).

Table III. *Urinary excretion of digoxin (μg) over 6 days after administration**

Subject	*0.4 mg in water*	*0.5 mg in tablets*	*0.4 mg in capsules (7.5 minim)*	*0.4 mg in capsules (4 minim)*
S.	204.6	187.0	247.8	264.2
P.	227.8	256.2	239.4	228.5
M.	238.3	294.9	285.1	283.0
C.	226.5	212.5	218.2	220.0
B.	164.4	166.5	219.2	193.3
A.	194.2	183.1	209.8	215.3
W.	229.6	236.9	260.1	261.8
Mean	212.2	219.6	239.9	238.0
SEM	9.9	17.3	10.1	12.2
CV	12.3	20.8	11.2	13.5

*Range of values with each treatment is indicated by standard error of the mean (SEM) and coefficient of variation (CV).

illness, and none was taking medication other than oral contraceptives.

All received the single-dose treatments in randomized sequence, each separated by at least 14 days. Treatments were administered at 9.0 A.M. after an overnight fast, and 100 ml of tap water was swallowed in conjunction with treatments 2 and 3. Nothing else was allowed by mouth for a further 3 hr. Urine was collected in 24-hr periods for 10 days after administration

Table IV. *Total urinary digoxin excretion (μg) over 10 days*

Subject	0.5 mg digoxin iv	0.5 mg digoxin U.S. Lanoxin tablets	0.4 mg digoxin capsules
Th.	423	305	298
Ba.	380	308	314
C.	382	220	260
G.	359	311	322
P.	378	308	300
P.S.	487	348	394
Ta.	409	287	315
M.	334	239	288
D.	298	237	250
To.	357	233	223
A. S.	390	380	332
Be.	452	301	297
Mean	387	290	299
±SEM	15	14	12
CV(%)	13	17	14

SEM: standard error of the mean.
CV: coefficient of variation.

of each treatment. Completeness of urinary collection was confirmed by determination of urinary creatinine excretion.

Assay and statistical evlaution. Plasma was quickly separated from blood samples and stored at 4° C. Aliquots of urine were obtained and similarly stored as soon as available. Digoxin was determined in all samples in triplicate by radioimmunoassay using the commercially available Lanoxitest-gamma kit (Wellcome Reagents Ltd), in which the tracer is an iodinated tyrosine derivative of digoxin.* Standards and reference human plasma or urine were included in each assay run. Statistical significance of differences was assessed by parametric analysis of variance.

Results

No subject reported nausea or other unpleasant symptoms following any treatment.

First experiment. As illustrated in Fig. 1, mean plasma concentrations were consistently higher during the first 7 hr after administration of either encapsulated preparation than after solution or tablets. Peak concentrations showed the greatest differences, as shown in Table I.

*Lader, S., Court, G., Johnson B. F., and Hurn, B. A. C.: Radioimmunoassay of digoxin with iodinated tracer. Scand. J. Clin. Lab. Invest. **29**:Suppl. 126, 1972.

Table V. *Individual percentage absorption of digoxin from tablets and from capsules*

Subject	Digoxin tablets	Digoxin capsules
Th.	72	87
Ba.	81	103
C.	58	85
G.	87	112
P.	82	99
P. S.	71	101
Ta.	70	96
M.	71	108
D.	80	105
To.	65	78
A. S.	98	107
Be.	67	82
Mean	75.1	96.9
±SEM	3.1	3.3

SEM: standard error of the mean.

The capsules of differing solvent content produced similar peak concentrations that were higher than those obtained with either solution or tablets ($p < 0.01$). Despite the higher digoxin dose administered, tablets produced the lowest peak concentrations ($p < 0.05$). Peak concentrations occurred between 0.5 and 1.75 hr after administration, and there was no significant difference in the mean time after treatments.

As shown in Table II, both types of capsule produced greater ($p < 0.01$) areas under the 24-hr plasma concentration curve than either tablets or solution. The latter did not significantly differ from each other.

Urinary excretion of digoxin is shown in Table III. The two types of capsule produced similar mean values, which were higher ($p < 0.05$) than for solution at 6 days. Tablets and solution did not significantly differ.

Second experiment. Ten days' cumulative urinary excretion of digoxin is indicated in Table IV. Although similar amounts of urinary digoxin appeared over 10 days after each oral treatment, a greater proportion of injected dose was recovered after capsules, the respective mean values being 75% for capsules and 58% for tablets ($p < 0.01$). After capsules, digoxin recovery was not significantly less than after injection of digoxin (77.4%).

For each individual, intestinal absorption was calculated by expressing the percentage of orally administered dose excreted as a proportion of that percentage excreted after injection. As shown in Table V, mean values for capsules and tablets were different ($p < 0.01$).

Discussion

Intestinal absorption of digoxin occurs more rapidly and to a greater extent from the experimental formulation encapsulated in soft gelatin than from an aqueous solution. The most apparent difference was in rate of absorption, indicated by the substantially higher peak plasma concentrations following ingestion of capsules. However, extent of absorption appears to correlate well with rate of absorption from oral digoxin preparations, and the experimental capsules were no exception. More digoxin was absorbed from the capsules than from an equal dose ingested in solution or from a larger dose in tablet form. Indeed, in the healthy volunteers studied, digoxin absorption from capsules was virtually complete. The selected tablets are known to be of consistently high bioavailability,[8] but absorption of digoxin was demonstrated to be less than that from solution. Tablets of higher dissolution rate, i.e., Lanoxin tablets manufactured in the United Kingdom, have been shown to have comparable bioavailability to digoxin in aqueous solution,[6] and it may therefore be inferred that the experimental capsule formulations are of greater bioavailability than any digoxin tablets. Comparison of mean area under curve determinations or 6 days' urinary excretion suggests that, respectively, 20% or 13% more digoxin is absorbed from capsules than from solution. There was a 2-fold variation of digoxin concentration in the encapsulated solution in the differing experimental capsules. However, altering the volume of solvent did not affect the enhanced bioavailability of the capsules.

It was anticipated that encapsulation of digoxin in solution would provide a formulation of excellent bioavailability, but enhanced absorption by comparison with solution was unexpected. It appears that capsules offer more complete absorption than any other oral preparation. It is possible that certain digoxin solvents could facilitate intestinal transport, and indeed rate and extent of absorption have been shown to be greater from pediatric elixir than from tablets of excellent bioavailability.[4] However, the nonaqueous solvents in elixir, ethyl alcohol, and propylene glycol are present only in minor quantities in the experimental capsules, and there is no published information on any possible influence of polyethylene glycol on digoxin absorption. It is equally possible that the soft gelatin capsule wall might be responsible for the enhanced bioavailability. Some degree of inactivation of digoxin is caused by gastric acid,[1, 7] and encapsulation might reduce this effect to some extent. If a capsule wall factor is responsible for enhanced absorption, it must be specific to soft gelatin or to an interaction with digoxin in solution, as hard gelatin encapsulation of a solid digoxin formulation of ultrarapid dissolution rate did not increase bioavailability.[6]

As was noted with pediatric elixir,[4] the enhanced digoxin absorption from soft gelatin capsules was associated with an exaggerated peak plasma concentration. Some authorities have expressed concern that transient elevation of plasma digoxin level might cause toxic effects in some patients.[3, 10] There is marked

individual variability in susceptibility to nausea, which usually occurs at the time of peak plasma concentration. Although no subject experienced any gastrointestinal symptom with any treatment in the reported study, it is possible that clinical use of soft gelatin capsules might be associated with an increased incidence of nausea. However, as recently reviewed,[2] there is no evidence to support fears that cardiac dysrhythmias might be more frequent during periods of transient elevation of plasma digoxin concentration.

There is considerable individual variability in intestinal absorption of digoxin, even from tablets of very high dissolution rate.[4] It has been shown[6] that a substantial increase in the mean extent of absorption from an oral preparation may be associated with reduction in the between-individual variability. Using coefficients of variation as measures of between-subject variability, the reported studies offer further confirmation of this relationship. Although of good bioavailability, the digoxin tablets produced higher coefficients of variation both for urinary measures of absorption and for area under plasma concentration curve determinations. Urinary excretion was equally consistent between subjects following intravenous or capsule administration of digoxin. It might be anticipated that the soft gelatin formulation would produce a more consistent and predictable response than digoxin tablets, but fairly widespread clinical application will be necessary to test this.

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