

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 18118**

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**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

Digoxin Solution in Capsule  
0.05, 0.1 & 0.2 mg  
Lanoxicap  
NDA 18-118

Burroughs Wellcome Co.  
Research Triangle Park, N.C.  
Submission Dated:  
January 9, 1978

### REVIEW OF 9 BIOAVAILABILITY STUDIES

A new dosage form, digoxin solution in capsule, was developed to improve intestinal absorption of digoxin.

Submitted are 9 bioavailability studies including single dose and multiple dose studies.

#### Overall Recommendation:

Increased extent and rate of absorption for Lanoxicaps when compared with those for Lanoxin tablets was demonstrated in single dose studies in either fast condition (#1, #3, #4, and #5) or in postprandial condition (#2) on normal human subjects.

There were no statistically significant differences of minimum digoxin plasma concentration in steady-state for 0.2 mg capsule or 0.25 mg digoxin tablet in study 1-a. However, the steady-state digoxin concentration for 0.2 mg capsule is approximately 10% and 14% lower than that of 0.25 mg U.K. digoxin tablets (dissolution rate of 97% in 2 hours) in normal subjects (#6) and cardiac patients (#9) respectively.

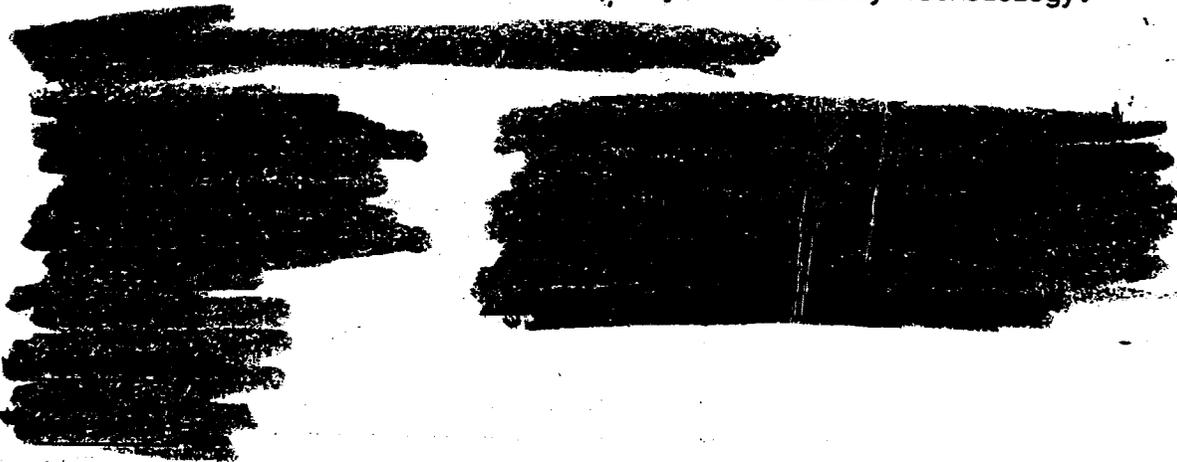
The mechanism for enhanced bioavailability of digoxin capsule was not clear. Studies #8 and #7 demonstrated that neither the presence nor the physical properties of capsule wall affected the bioavailability of digoxin when it was given in filling solution. However, it was conflicting with the observation from study #2 which suggested digoxin capsule was more bioavailable than digoxin elixier.

The studies suggested that inter-and intra-subject variations in bioavailability parameters might be reduced for capsule as compared with tablet formulation. A reduced intersubject variation in single dose study for capsule was observed for study #4, however, approximately the same variation for capsule and tablet was observed in study #1, #2, #3, and #5. The intersubject variation of steady state digoxin levels for capsule in multiple dose study #6 was less than those for tablets, however, approximately equal intersubject variation was observed in study #9. A less day-to-day variation or intrasubject variation was observed for study #9 but equal variation was observed in study #6.

The safety issue of higher peak digoxin level should be reviewed by the medical officer.

OVERALL COMMENTS:

1. Because of the assay limitation at the time when the study was conducted, plasma samples were collected and estimated for less than one half-life, from pharmacokinetics point of view, bioavailability can not be accurately accessed. However, the trend of the relative bioavailability is demonstrated.
2. The submission may suggest a reduced inter and intra-subject variation for digoxin capsules as compared to digoxin tablets, however, it is not conclusive; since some of the studies demonstrated reduced inter and intra-subject variation and some do not. A possible explanation for the discrepancy is the assay methodology.



The purpose of the study was to determine the bioavailability of soft gelatin capsule, tablet and solution under steady-state conditions in normal subjects. Three studies were performed by Dr. J. Lindenbaum, Columbia University, N.Y.

Study a:Study Design:

Eight volunteers (22-46 years old) were involved. Each subject received the following formulations in a randomized Latin square design.

A: 0.2 mg soft gelatin capsule [REDACTED]

B: 0.2 mg digoxin tablet with a rapid dissolution rate [REDACTED]

C. 0.25 mg digoxin tablet with a rapid dissolution rate [REDACTED]

D. 0.25 mg digoxin tablet with dissolution rate of [REDACTED]

A two-weeks washout period was allowed between the treatments. Each was administered as follows:

Day 1: Two tablets or capsules at 8:00 a.m. in the fasting state and at 4:00 p.m. and 12 midnight.

Day 2: Two tablets or capsules at 8:00 a.m. in the fasting state.

Day 3-9: One tablet or capsule at 10 a.m. and at 5:00 p.m., 2 to 4 hours after meals.

Serum was obtained on Day 1 at 0, 0.5, 1, 1.5, 2, 3 and 6 hours after dosing and on days 2, 8, 9, and 10 at 9:00 a.m. Twenty-four hour urine collections were obtained on Day 1, and on Day 9 for most of the subjects.

Results:

1. Mean and coefficient of variation (%) of serum digoxin levels and bioavailability parameters are shown in the following table:

Serum levels (ng/ml) at	capsule	tablet	tablet	tablet
	0.2 mg A	0.2 mg B	0.25 mg C	0.25 mg D
0.5 hr	1.81 (127)	0.74 (157)	1.18 (98)	0.64 (102)
1	2.74 (38)	1.20 (77)	2.05 (70)	1.55 (62)
1.5	2.14 (42)	1.59 (46)	1.82 (37)	1.62 (38)
2	1.55 (38)	1.37 (22)	1.78 (27)	1.42 (20)
3	1.09 (31)	0.86 (29)	1.34 (33)	1.18 (40)
6	0.56 (21)	0.45 (38)	0.62 (23)	0.63 (22)
25	3.54 (46)	2.39 (48)	3.10 (34)	2.37 (35)
Cmax ng/ml	3.34 (45)	2.08 (28)	2.68 (32)	2.12 (24)
Tmax hr	1.25 (64)	1.50 (60)	1.68 (54)	1.75 (49)
AUC (0-6 hr)	7.52 (19)	5.18 (15)	7.47 (16)	6.27 (11)
Ae (day 1) mcg	273 (22)	206 (16)	248 (15)	260 (28)
Cpss(days 8-10)ng/ml	1.08 (17)	0.91 (22)	1.02 (17)	1.17 (29)
Ae (day 9) mcg	255 (20)	203 (16)	242 (18)	240 (22)

There were significant differences in AUC (0-6 hrs) between treatments A and D, and between treatments B and C.

The cumulated urinary excretion and serum levels of digoxin are lower for treatment B compared with treatment A, C and D.

A possible significant differences ( $p = 0.08$ ) were observed for steady state serum levels of digoxin for the 4 treatments.

Recommendation:

This is a preliminary study suggesting that digoxin capsule has greater bioavailability than tablet of equivalent dose.

Comments:

1. The study suggested that digoxin capsule was absorbed faster and more than tablets.
2. There were no significant differences in the coefficient of variation for bioavailability parameters and digoxin plasma levels between treatments.
3. From pharmacokinetics point of view, the bioavailability derived from AUC of plasma levels 0-6 hours (less than one half-life) is not accurate, however, it does reveal the relative trend of bioavailability for formulations tested.
4. Theoretically, amount of digoxin excreted in 24 hour urine in steady state is a good estimate for bioavailability, however, because of the greater intersubject variations (partly may due to be cross reactivity of the assay method) and small number of subjects used, the study does not have the power (0.8) of detecting 20% significant differences between the treatment.

Study b:Study design:

Six subjects were involved in a randomized crossover design. Each subject received treatment A and treatment B as described for study a.

Results:

Mean and coefficient of variation (%) of steady-state serum levels and amount excreted in the urine obtained from study a and study b are as following:

	A (0.2 mg capsule)		
	Study a	Study b	a & b*
C <sub>ss</sub> ng/ml	1.08 (17)	0.96 (26)	1.03 (20)
Ae (day 1)	273 (22)	216 (31)	249 (27)
Ae (day 9)	255 (20)	206 (33)	230 (27)

	B (0.2 mg capsule)		
	Study a	Study b	a & b*
C <sub>ss</sub> ng/ml	0.91 (22)	0.89 (17)	0.90 (19)
Ae (day 1)	206 (16)	198 (17)	203 (17)
Ae (day 9)	203 (16)	161 (33)	183 (25)

\*pooled data of study a and b.

There were no statistical significant differences (ANOVA) for steady state serum levels and urinary excretion of digoxin between capsule and tablet in study b.

When paired t-test was performed on pooled data of study a and b, there were statistical significances in steady state digoxin serum levels and urinary excreted digoxin between 0.2 mg capsule and 0.2 mg tablet.

Recommendation:

The study suggested that digoxin capsule might have greater bioavailability than tablet, however, it is not conclusive.

Comments:

1. Because of the intersubject variations and small number of subjects used in this study, the study is inconclusive.
2. Paired t-test is not appropriate for a crossover design since it ignores period effects.

Study c:

Ten volunteers were given a single oral dose of 0.4 mg of the following formulations following a high fat meal, serum samples were obtained from 0 to 6 hour and a 24 hour urine was collected.

A. 0.2 mg soft gelatin digoxin capsule (Lot 919-I, CTM #1746)

E: Digoxin solution as prepared for soft gelatin Capsule in A.

F: Lanoxin R brand Elixier Peadiatric.

Results:

Mean and coefficient of variations of serum levels and bioavailability parameters of digoxin:

	Capsule	Elixir	Solution
Serum levels			
ng/ml at 0.5	2.3 (83)	2.1 (62)	2.0 (65)
1	2.2 (55)	1.8 (28)	2.0 (55)
1.5	1.9 (37)	1.3 (23)	1.2 (25)
2	1.3 (31)	0.9 (22)	1.0 (20)
3	0.9 (33)	0.6 (33)	0.6 (17)
6	0.6 (100)	0.4 (25)	0.4 (25)
C <sub>max</sub> ng/ml	3.1 (39)	2.4 (46)	2.6 (31)
T <sub>max</sub> hr	0.8 (50)	0.7 (43)	0.8 (63)
AUC (0-6 hr)			
ng/ml hr.	6.8 (38)	5.2 (29)	5.1 (23)
A <sub>e</sub> (24 hrs) mcg	100.3 (22)	90.9 (17)	83.4 (19)

There were statistically significant differences in AUC (0-6 hr) among capsule, elixier and solutions, no differences in urinary excretion for 24 hours.

Recommendation:

The study suggests that digoxin capsule has possibly greater bioavailability than digoxin elixir and digoxin simple solution in post prandial subjects.

Comments:

1. Digoxin capsule appeared to have greater bioavailability as judged from AUC (0-6 hrs). However, the absolute bioavailability can not be obtained from AUC (0-6 hr), neither from urinary excretion data for 24 hours.

Study 2: By Dr. John Lindenbaum, Columbia Presbyterian Hospital, N.Y.

Objective:

To examine the absorption characteristics and bioavailability of an encapsulated digoxin solution in postprandial normal subjects.

Study Design:

Twelve healthy subjects were involved in the 3-way crossover study each subject received a single oral dose of 0.4 mg of the following formulations:

1. Soft gelatin capsules [REDACTED]

2. 0.4 mg of digoxin dissolved in [REDACTED]

3. 0.2 mg digoxin tablets [REDACTED]

A two-week washout period was allowed between the treatments.

Each of the formulations was ingested with 250 ml of water immediately after breakfast. Blood was collected at 0, 0.5, 1, 1.5, 2, 3, 4, and 6 hour. Urine samples were collected over 6 days.

### Analytical Method:

Digoxin concentrations in serum and urine were determined by a modification of the radioimmunoassay method of Hayes Butler and Gersony.

### Results:

Mean and coefficients of variation (%) of serum digoxin and bioavailability parameters:

	Capsule	Solution	Tablet
Plasma levels			
ng/ml at 0.5 hr	2.21 (66.9)	1.23 (39.7)	1.03 (65.5)
1	2.22 (43.1)	1.43 (22.5)	1.58 (41.8)
1.5	1.65 (20.6)	1.35 (15.0)	1.28 (22.1)
2	1.25 (22.7)	1.19 (23.5)	1.03 (19.5)
3	0.90 (29.5)	0.96 (35.1)	0.82 (19.7)
4	0.64 (24.9)	0.71 (30.9)	0.70 (31.5)
6	0.50 (20.9)	0.48 (31.4)	0.48 (29.9)
Cmax ng/ml	2.69 (34.5)	1.58 (20.6)	1.61 (40.4)
Tmax hr	0.83 (55.2)	1.22 (56.2)	1.13 (27.6)
AUC (0-6 hrs)			
ng/ml x hr	6.37 (20.0)	5.40 (20.2)	5.07 (21.6)
Ae (6 days) mcg	239 (12.1)	209 (10.9)	219 (11.2)

There were statistically significant differences for Cmax, AUC and 6-day urinary excretion between capsules and solution and tablet.

### Recommendation:

The study demonstrated that digoxin capsule had greater bioavailability than solution and tablets of equivalent dose.

### Comments:

1. Earlier and higher peaks were observed for digoxin capsule than tablet and solution.
2. Greater bioavailability of digoxin capsule was observed when bioavailability was measured by AUC (18 - 27% larger than solution and tablet, respectively) than when measured by 6-day cumulative urinary excretion, CUE, (16 and 10%, respectively). The discrepancy was possibly from the estimation of bioavailability from incomplete plasma profiles and crossreactivity of radioimmunoassay.

3. There were no differences in coefficient of variations for serum digoxin level or bioavailability parameters between the treatments.

Study #3 (Study No. 75-178F, 75-179F, 75-182F)

Objective:

The objective of this study was to determine the absolute bioavailability of Lanoxicaps. Three studies which were conducted by Dr. P. Binnion (Pennsylvania Hospital, Pa.), Dr. J. Doherty (V. A. Hospital, Arkansas) and DR. F. Marcus (Arizona Medical Center, Arizona) were included and the data were pooled for statistical analysis.

Study Design:

1. Each clinical center enlisted six healthy subjects for the study.
2. Subjects were receiving the following formulations:
  - A. Eight of 0.05 mg Lanoxicaps brand digoxin capsules
  - B. Four of 0.10 mg Lanoxicaps brand digoxin capsules
  - C. Two of 0.20 mg Lanoxicaps brand digoxin capsules
  - D. An intravenous infusion of 0.4 mg injectable digoxin in 10 ml saline.
  - E. Two 0.20 mg reference digoxin tablets
  - F. USP digoxin reference solution containing 0.4 mg digoxin in 200 ml of water

3. The study conducted by Dr. Marcus was a six-way crossover design. The other two studies by Dr. Binnon and Dr. Doherty were carried out as a balanced incomplete block design, each subject received 5 treatments in changeover random sequence. At least 2 weeks were elapsed between each treatment.
4. Subject were fasted overnight before dosing drug orally and remained fasting for 4 hours after dosing.
5. Blood samples were taken at 0, 0.5, 1, 1.5, 2, 3, 4 and 6 hours and urine was collected for 6 consecutive 24 hour periods after the medication.
6. Radioimmunoassay method was used for assay.

#### Results:

1. Mean and coefficient of variation (%) of serum digoxin level and bioavailability parameters:

Doherty:

	I.V.	Solution	Capsule 8X 0.05	Capsule 4X 0.1	Capsule 2X 0.2	Tablet 2X 0.2
0.5 hr	5.36 (35)	3.01 (29)	4.13 (24)	3.53 (69)	3.81 (31)	1.24 (40)
1	3.36 (24)	2.73 (41)	3.93 (19)	3.73 (24)	3.64 (16)	1.92 (31)
1.5	2.27 (24)	2.06 (33)	2.49 (18)	2.76 (20)	2.46 (9)	1.50 (33)
2	1.72 (33)	1.45 (38)	1.72 (26)	1.96 (17)	1.79 (13)	1.35 (35)
3	1.19 (39)	1.22 (34)	1.05 (38)	1.29 (25)	1.18 (18)	0.97 (29)
4	1.04 (38)	0.93 (38)	0.89 (31)	1.07 (29)	0.97 (23)	0.75 (13)
6	0.80 (26)	0.67 (28)	0.63 (16)	0.61 (13)	0.67 (19)	0.63 (29)
t <sub>max</sub> hr	-	0.70 (39)	0.80 (34)	0.80 (34)	0.80 (34)	1.10 (50)
C <sub>max</sub> ng/ml	5.36 (35)	3.13 (27)	4.54 (12)	4.44 (34)	4.18 (18)	1.98 (28)
AUC (0-6 hr)	10.35 (30)	8.28 (31)	9.60 (18)	10.01 (19)	9.61 (10)	6.09 (21)
Ae mcg	250 (6.1)	188 (6.9)	205 (7.0)	204 (6.5)	209 (8.4)	174 (6.4)

Marcus:

0.5 hr	3.76 (20)	2.08 (51)	3.49 (30)	2.79 (50)	3.65 (15)	1.35 (16)
1	4.94 (24)	2.08 (26)	2.76 (24)	2.46 (18)	2.35 (17)	1.87 (11)
1.5	2.23 (20)	1.36 (33)	1.58 (26)	1.59 (35)	1.42 (20)	1.40 (18)
2	1.28 (20)	0.95 (32)	1.07 (19)	1.09 (35)	0.96 (13)	1.14 (30)
3	0.67 (19)	0.69 (35)	0.74 (19)	0.66 (27)	0.69 (14)	0.80 (23)
4	0.53 (23)	0.61 (22)	0.63 (19)	0.55 (16)	0.55 (14)	0.58 (20)
6	0.33 (32)	0.39 (28)	0.42 (18)	0.42 (13)	0.40 (23)	0.45 (17)
T <sub>max</sub>	1 (0)	0.67 (38)	0.58 (35)	0.67 (39)	0.5 (0)	1.0 (30)
C <sub>max</sub>	4.94 (24)	2.46 (33)	3.67 (21)	3.31 (22)	3.65 (15)	1.88 (10)
AUC	8.23 (18)	5.49 (22)	6.83 (13)	6.14 (13)	6.36 (10)	5.30 (15)
	240 (6.0)	204 (6.7)	239 (2.2)	232 (5.6)	247 (4.0)	206 (4.2)

## Binnon:

0.5	3.74 (27)	2.33 (29)	1.67 (109)	3.14 (40)	2.53 (33)	0.97 (18)
1	6.00 (31)	2.16 (27)	3.29 (25)	2.93 (30)	3.21 (26)	1.31 (30)
1.5	2.13 (20)	1.44 (27)	2.05 (26)	1.61 (28)	2.04 (31)	1.19 (35)
2	1.27 (24)	0.97 (29)	1.29 (31)	1.00 (32)	1.33 (38)	0.87 (23)
3	0.73 (26)	0.71 (39)	0.75 (39)	0.64 (34)	0.78 (29)	0.61 (20)
4	0.50 (23)	0.56 (17)	0.55 (43)	0.52 (26)	0.61 (37)	0.45 (22)
6	0.29 (26)	0.31 (33)	0.27 (53)	0.26 (46)	0.29 (28)	0.20 (35)
Tmax	0.90 (25)	0.7 (39)	0.9 (25)	0.70 (39)	0.9 (25)	0.9 (46)
Cmax	6.0 (31)	2.44 (25)	3.46 (29)	3.70 (25)	3.47 (14)	1.38 (24)
AUC	8.67 (21)	5.55 (22)	6.32 (29)	6.27 (23)	6.88 (21)	3.87 (18)
Ae	279 (0.9)	239 (10)	255 (2.3)	279 (4.3)	258 (3.1)	209 (7.1)

## Pooled Pharmacokinetic parameters from 3 centers:

	I.V.	Solution	Capsule 8X 0.05	Capsule 4X 0.1	Capsule 2X 0.2	Tablet 2X 0.2
No. of Sub- jects	15	16	16	16	16	16
Tmax	0.83 (30)	0.69 (36)	0.75 (34)	0.72 (36)	0.72 (36)	1.0 (41)
Cmax	5.41 (30)	2.67 (30)	3.88 (23)	3.79 (30)	3.76 (17)	1.76 (25)
AUC	8.95 (24)	6.39 (33)	7.54 (27)	7.40 (31)	7.55 (23)	5.11 (25)
Ae	256 (12)	211 (20)	233 (12)	237 (18)	237 (15)	199 (15)

Higher peak concentrations and greater AUCs were observed for I.V. dosing. Tablets were the least bioavailable dosage form as judged from AUC and urinary excretion data.

Comments:

1. The study demonstrated that capsule formulations is more bioavailable than tablet and solution dosage forms.
2. The statistical analysis of pooled data from 3 clinical centers is acceptable (see attached reviews by Division of Biometrics).
3. No indication of reduced inter-or intra-subject variation in bioavailability parameters, was observed for capsule dosage form as compared to tablet or solution.

Recommendation:

The study is acceptable.

Study 4 - By Johnson et. al. at Wellcome Research Lab.  
Beckenham, England.

Objective:

The objective of the study was to compare the absorption of digoxin from two capsules of differing volume of solvent, aqueous digoxin solution and a reference tablet.

Study Design:

Eight healthy volunteers were used. Seven finished the study. Each subject received 4 treatments in a randomized crossover design. Subjects were fasted overnight before administration of the drug and continued fasting for another 3 hours. Urine were collected in 24 hour period for 6 days and blood were collected at 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 4, 7 and 24 hours after dosing.

The following were the 4 treatments given to the subjects:

- A. Digoxin 0.4 mg administered orally as a solution of U.S.P. digoxin
- B. Digoxin 0.5 mg administered orally as 2 of United States Lanoxin tablets
- C. Digoxin 0.4 mg administered orally as two experimental capsules of 7.5 minims solvent content
- D. Digoxin 0.4 mg administered orally as two experimental capsules of

#### Analytical Methods:

Determination of digoxin concentration in plasma and urine was carried out by radioimmunoassay. (J. Clin. Lab. Invest. 29, suppl. No. 126, 1972).

#### Results:

1. Mean and coefficient of variation for plasma digoxin levels (ng/ml) and bioavailability parameters are:

	Solution	Tablet	Capsule (7.5)	Capsule (4)
0	0.07 (60)	0.04 (54)	0.05 (46)	0.05 (46)
0.5	2.36 (19)	1.25 (64)	2.26 (58)	1.96 (100)
0.75	2.78 (21)	1.79 (39)	4.15 (14)	2.88 (46)
1	2.49 (20)	1.84 (27)	3.78 (14)	3.40 (28)
1.25	2.15 (25)	1.82 (28)	3.20 (12)	3.10 (14)
1.5	1.95 (26)	1.62 (31)	2.58 (14)	2.79 (18)
1.75	1.60 (33)	1.54 (33)	2.19 (15)	2.45 (25)
2	1.40 (19)	1.40 (29)	1.87 (20)	2.29 (29)
4	0.67 (23)	0.73 (34)	0.72 (17)	0.78 (14)
7	0.39 (27)	0.45 (32)	0.48 (16)	0.47 (18)
24	0.34 (29)	0.31 (24)	0.33 (17)	0.34 (20)
C <sub>max</sub>	2.91 (16)	2.07 (24)	4.42 (13)	3.97 (17)
AUC (0-24)	13.67 (15)	12.61 (27)	16.40 (13)	16.40 (13)
A <sub>e</sub> (6 days)mcg	212.2 (12)	219.6 (21)	239.9 (11)	238.1 (14)
% of dose	53	44	60	60

There were significant differences (ANOVA) in Cmax, AUC and amount excreted in the urine between the treatments.

Apparently, there were less coefficient of variations for plasma digoxin levels and bioavailability parameters for capsule formulations than for tablet.

Greater bioavailability for digoxin capsules were evidenced by greater AUC 0-24 hr and greater urinary excreted digoxin in 24 hours.

Comments:

1. Faster absorption rate and greater bioavailability were observed for capsule formulation than those for tablets and solution.
2. Possibly less intersubject variations in plasma levels were observed for capsules than those for tablets and solution as reflected by less coefficient of variations in the data.

Study 5

The Pharmacokinetics of beta-methyl digoxin compared with digoxin tablets and capsules by B.F. Johnson et. al.

Objective:

The objectives of this study were to compare the percentage intestinal absorption of digoxin from capsules and tablets and beta-methyl digoxin from tablets. The study was carried out in Wellcome Research Laboratories, Beckenham, Kent, England.

Study Design:

1. Twelve healthy volunteers (9 males and 3 females) were used.

2. Each volunteer received the following 5 treatments in a randomized sequence, each treatment separated by at least fourteen days.

A: 0.5 mg of digoxin as 2 ml of Lanoxin injection

B: 0.5 mg of beta-methyl digoxin as

C: 0.5 mg of digoxin as two Lanoxin tablets

D: 0.5 mg of beta-methyl digoxin as 5 Lanitop tablets

E. 0.4 mg of digoxin as two experimental soft gelating capsules (Lanoxicaps) each of

3. Subjects were fasted overnight before medication and fasting continued for a further 3 hours after medication.

4. Urine was collected in 24 hours periods for 10 days, after each treatment.

Assay:

Digoxin and methyl digoxin in the urine were determined by radioimmunoassay method using Lanoxitest-gamma kit (Wellcome Reagents LTD). The antibody binds equally with digoxin and analogues in which the genin component of the molecule is intact.

Results:

Mean and coefficient of variation (%) for bioavailability parameters:

	Digoxin I.V.	BMD I.V.	Digoxin tablets	BMD tablets	Digoxin capsules
Ae (10-days)	387.3(13.2)	352.6(12.8)	289.8(16.9)	303.8(13.1)	299.3(14.6)
% absorbed*	100	100	75.1(14.3)	86.9(13.5)	96.9(11.6)
Urinary t 1/2 (hr)	34.9(6.3)	39.8(5.5)	35.4(5.3)	39.4(7.2)	35.6(5.9)

\*As compared with I.V. dose.

There were significant differences in the amount of digoxin excreted in 10 days between the treatment.

Comments:

1. Radioimmunoassay method (RIA) is not specific for digoxin, it also measures the cardioactive metabolites.
2. Enhanced absorption of digoxin from digoxin capsule was demonstrated.
3. The coefficient of variation for digoxin capsule and tablet was 15% and 17% respectively, therefore the significance of the improvement of intersubject variation between tablet and capsule is limited.
4. There were 58% and 75% of the dose was excreted as digoxin in urine in 10 days for digoxin tablet and digoxin capsules respectively.

Study 6:

The Comparability of Dosage Regimens of Lanoxin tablets and Lanoxicaps by B. F. Johnson in Wellcome Research Laboratories, England.

Objective:

The objective of this study was to compare the absorption of digoxin from soft gelatin capsules and tablets in the non-fasting state and over several days.

Study Design:

Ten healthy volunteers aged 19 to 28 years were used. Each received the following treatments in a randomized sequence:

A. 0.25 mg Lanoxin tablets

B. 0.20 mg digoxin in a solution

Each treatment was ingested at 09 h 30 min. and 21 hr 30 min. daily for 14 days.

Plasma samples for determination of digoxin concentration were obtained at 09.00 hour on each of the last three days of both periods of treatment. And on one day the subjects fasted overnight and during the following morning, additional plasma samples were collected at 0.5, 0.75, 1., 1.25, 1.5, 2, 4, and 7 hour after the morning dose. All urine passed during the last two days of each treatment period was collected in 4 dosage intervals.

Assay:

Digoxin in the samples was determined by radioimmunoassay method using Lanoxitestgamma kit. (Wellcome Reagents LTD).

Results:

1. Mean and coefficient of variation for plasma digoxin level and bioavailability parameters are:

	Lanoxin tablet (0.25 mg)	Lanoxicap (0.2 mg)	Pvalue*
D	1.16 (25)	1.02 (25)	
0.5	2.09 (34)	3.05 (29)	
0.75	270 (27)	3.41 (9)	
1	2.81 (19)	3.16 (11)	
1.25	2.90 (17)	3.05 (12)	
1.5	2.91 (16)	2.76 (14)	
2	2.72 (16)	2.40 (14)	
4	1.64 (27)	1.46 (22)	
7	1.40 (25)	1.09 (23)	
Cmin (ng/ml)	1.07 (22)	0.95 (16)	0.09
Cmax (ng/ml)	3.10 (15)	3.51 (8.1)	0.09
Tmax (hr)	1.15 (28)	0.78 (38)	0.05
AUC (0-7 hr)	13.8 (17)	13.1 (13)	N.S.
Ae (12 hr) mcg	143.6 (12)	130.9 (10)	0.05

P value\* was obtained by ANOVA

- Paired t-test was performed, there were no statistical significant differences for AUC, Cmin, Cmax between the treatments. There were significant differences in amount excreted and Tmax between the treatment (p 0.05). The same results were obtained from ANOVA.
2. There were no differences in the averaged day to day variations (14%) for the minimum plasma levels of digoxin at steady state.
  3. The coefficients of variation for bioavailability parameters is slightly greater for Lanoxin tablet than those for Lanoxicap.
  4. At steady-state, 57 and 65% of the dose were excreted in the urine as digoxin for Lanoxin tablet and Lanoxicap respectively.

Comment:

1. The averaged steady-state plasma level (C<sub>min</sub>) for Lanoxicap is 89% of that for Lanoxin tablet and the averaged amount of digoxin excreted in 12 hours for Lanoxicap is 91% of that for Lanoxin tablets.
2. There were no differences in day to day variations for plasma steady-state level between the treatments.
3. Statistically, there were no differences in AUC (0-7 hr) between Lanoxicap and Lanoxin. However, AUC (0-7 hr) tends to underestimate the real bioavailability for Lanoxin tablets than for Lanoxicap since the plasma digoxin levels for Lanoxin tablets at 7 hour is higher than Lanoxicaps.

Study 7:

Effects of storage upon in-vitro and in-vivo characteristics of soft gelatin capsules containing digoxin by B. F. Johnson, Wellcome Research Laboratories, Beckenham, England.

Objective:

The objective of the study was to determine that whether storage at different conditions would change the bioavailability of digoxin capsules.

Study Design:

1. Six healthy subjects aged 27 to 34 were used.
2. Each subject received a single dose of 0.6 mg of digoxin as the following treatments in a randomized Latin-square design.
  - A: 12 capsules of fresh made soft gelatin capsules.
  - B: 12 of soft gelatin capsules stored at 50° C for 10 months.
  - C: 12 of soft gelatin capsules stored at 37° C for 10 months.
3. Capsules were administered to the subject after an overnight fast and fast continued for another 3 hours after the medication. Two weeks were elapsed between the treatments.
4. Blood samples were collected at 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 5 and 7 hours and urine collected in 24 hours period for 6 days after the medication.

Assay:

Digoxin was determined in the samples by radioimmunoassay method using Lanoxitestgamma Kit (Wellcome Reagents LTD).

Results:

1. Dissolution profiles for capsules presented as % dissolved:

10 min. 20 30	0.05 mg			0.1 mg		0.2 mg	
	fresh	50(10 mon.)	370(10 mon.)	fresh	370(12 mon.)	fresh	370(12 mon.)
	89	66	10	108	68	104	103
	100	97	64	-	106	-	-
	100	100	92				

Dissolution rate was determined by the method described in the 1975 addendum to the British Pharmacopocia 1973.

2. The bioavailability parameters (Mean and coefficient of variation %):

	fresh 50C (10 mon.)	37°C (10 mon.)
C <sub>max</sub> ng/ml	5.3 (17)	5.4 (16)
AUC (0-2) ng/ml x hr	11.9 (19)	11.6 (17)
Ae (0-6 days) mcg	257.1 (16.1)	258.6 (9.2)
T <sub>max</sub> hr	0.73	0.75
		4.8 (19)
		10.7 (18)
		242.0 (11.1)
		0.96

No significant differences (ANOVA) in Peak plasma levels, AUC and urinary recovery among the three treatments.

Comments:

1. The study demonstrated that there were no statistical significant differences in C<sub>max</sub>, AUC and amount excreted for the three 0.05 mg digoxin capsule having different dissolution rates in 20 minutes. However, a delayed T<sub>max</sub> was observed for the capsule with the slowest dissolution rate.
2. The number of subjects used can not detect 20% differences in peak plasma concentration with a power of 0.8 and at significance level of 0.05. However, the study has a power of 0.8 to detect 20% differences in AUC and amount excreted in the urine.

Study 8 - Influence of soft gelatin on digoxin absorption: by B. F. Johnson, et. al.

Objective:

The objective of the study was to investigate the effect of the presence of soft gelatin on absorption of digoxin from solution.

Study Design:

Eight healthy volunteers aged between 19 to 53 years and weight between 57 and 99 kg were used in a randomized 4 way crossover design. Each subject received 0.6 mg digoxin in a solvent mixture containing

- A. 3 intact soft gelatin capsules each containing 0.2 mg digoxin followed by 100 ml of water.
- B. 3 soft gelatin capsules each containing 0.2 mg digoxin cut in half immediately before administration and followed by 100 ml of water.
- C. A solution of digoxin containing 0.6 mg digoxin, followed by 100 ml of water.
- D. 3 soft gelatin capsules each containing 0.2 mg digoxin, dissolved in 100 ml of water by heating to 37°C for a 5 minute period immediately prior to administration.

14 days were separated between treatments.

Plasma and urine samples were collected. Treatments were administered after an overnight fast and nothing else were allowed by mouth for a further 3 hours.

Assay:

Radioimmunoassay (RIA) method employing Lanoxitest gamma kit was used.

## Results:

Mean and coefficient of variation of plasma digoxin level and bioavailability parameters are:

Plasma level (ng/ml)	Intact	Cut	Filling	Dissolved
at 0 hr	0.05 (79)	0.04 (92)	0.04 (120)	0.08 (64)
0.5	5.03 (59)	6.67 (29)	6.01 (45)	6.92 (25)
0.75	5.65 (68)	6.00 (31)	6.31 (27)	5.99 (21)
1	4.75 (42)	5.03 (30)	4.93 (24)	4.90 (18)
1.25	4.18 (33)	3.98 (30)	4.08 (27)	4.09 (22)
1.5	3.63 (36)	3.50 (31)	3.67 (32)	3.40 (20)
2	2.56 (35)	2.61 (37)	2.70 (27)	2.59 (31)
3	1.62 (42)	1.42 (27)	1.70 (34)	1.75 (29)
5	0.97 (37)	0.94 (32)	0.93 (43)	0.84 (42)
7	0.84 (33)	0.71 (33)	0.78 (38)	0.77 (38)
Cmax ng/ml	6.56 (36)	6.89 (30)	6.78 (28)	7.10 (24)
Tmax hr	0.78 (43)	0.56 (21)	0.59 (13)	0.56 (12)
AUC (0-7 hr)	14.02 (28)	14.23 (28)	14.67 (29)	14.61 (24)
Ae (6 days)	278.1 (20)	295.6 (20)	309.3 (14)	290.5 (26)

There were no statistical significant differences (ANOVA) in the bioavailability parameters between the treatments.

Comments:

1. The study demonstrated that there were no differences for the formulations having the same solvent system. The power to detect 20% differences in AUC, C<sub>max</sub> and amount excreted in 6 days is greater than 0.8.
2. The averaged percent of dose excreted in the urine in 6 days were ranged from 46 to 52% of the dose for the 4 treatments. It appeared to be lower than study #4.

Study 9 - Evaluation of Digoxin capsules in outpatients -Objective:

The objective of the study was to compare the clinical effect and digoxin plasma levels of digoxin capsule and digoxin tablets in the patients.

Study design:

1. Twenty patients (9 males, 11 females, with creatinine clearance 37 to 120 ml/min) on maintenance therapy were used in a crossover design.
2. Each patient received either four weeks of digoxin tablets (Lanoxin, U.K., 0.125, 0.1875, 0.25, 0.375 or 0.5 mg) or of capsules (0.1, 0.15, 0.2, 0.3, or 0.4 mg) at 10.00 hour each day. At the end of the 4 weeks period, patient crossover to the alternate treatment.
3. The dose of the tablet was equal to the total previously received in a day, the capsule dose being 80% of this.
4. During the fourth week, the following investigations were carried out: 1) clinical assessment, 2) E.C.G., 3) serum creatinine and electrolyte concentrations and routine liver function tests.
5. Blood samples for digoxin assay were collected just before a dose, one during the third week and a third during the fourth week on each formulation.

Results:

1. Mean and coefficient of variation for serum digoxin level following treatments:

	Tablet	Capsule
Dose (mg)	0.27 (44)	0.22 (44)
Serum concentration (n mole/l)	1.30 (32)	1.12 (29)

2. Mean and coefficient of variation for serum digoxin concentration determined between the third and the fourth week for patients of each dosage form:

	Tablet	Capsule
Mean	0.24	0.12
S.D.	0.17	0.12
C.V. (%)	74	100

3. Linear regression of serum digoxin concentrations for the 3rd week and the 4th week:

	$r^2$	$a_0$	$a^1$
Tablet (n=20)	0.67	-0.064	1.07
Capsule (n=19)	0.78	0.236	0.82

4. There was a better correlation for tablets of creatinine clearance and dose required to maintain 1.30 n mole/l digoxin level.

Comments:

1. A slightly better correlation of serum digoxin level for capsule was observed. The mean of the intrasubject differences between the third and the fourth week was smaller for capsule, however, the coefficient of the variation for capsule was greater. It suggests that intrasubject variation was reduced for capsule.

*EDP*

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Pharmacokinetics Branch

cc: NDA Orig., HFD-150, HFD-525 (Dr. Chiang), Chron., Review,  
and Drug Files

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FINAL TYPED INITIALED BY JPSKELLY

*Edward D. Purich 7/9/80*