CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20405

PHARMACOLOGY REVIEW(S)

NDA 20-405

PHARMACOLOGY REVIEW OF ORIGINAL APPLICATION

C.A.Resnick, Ph.D.
6 November 1993

SUBMISSION DATE: 30 September 1993
CENTER RECEIPT DATE: 30 September 1993
REVIEWER RECEIPT DATE: 07 October 1993

SPONSOR: Burroughs Wellcome Co.
Research Triangle Park, NC

DRUG: Lanoxin (digoxin) Tablets

FORMULATION: Tablets containing 0.0625 mg, 0.125 mg, 0.1875 mg, 0.25 mg, 0.375 mg or 0.5 mg digoxin USP plus corn and potato starches, lactose and magnesium stearate. Dyes used in one or more of these tablet formulations include FD&C Yellow No.6. D&C Yellow No.10,

PHARMACOLOGICAL CLASS: Cardiac Glycoside.

PROPOSED INDICATION: Heart Failure in patients receiving angiotensin converting enzyme (ACE) inhibitors and diuretics or diuretics alone.

PROPOSED DOSAGE: According to proposed labeling, "a single initial dose of 500 to 750 mcg (0.5-0.75mg) of Lanoxin Tablets usually produces a detectable effect in 0.5 to 2 hours that becomes maximal in 2 to 6 hours. Additional doses of 125 to 375 mcg (0.125-0.375mg) may be given cautiously at 6 to 8 hour intervals until clinical evidence of an adequate effect is noted. The usual amount of Lanoxin Tablets that a 70 kg patient requires to achieve 8 to 12 mcg/kg peak body stores is 750 to 1250 mcg (0.75 to 1.25mg)." As for maintenence dosing, "therapy is generally initiated at a dose of 250 mcg (0.25mg) once daily in patients under age 70 with good renal function, at a dose of 125 mcg (0.125mg) once daily in patients over age 70 or with impaired renal function, and at a dose of 62.5 mcg (0.0625mg) in patients with marked renal impairment. Doses may be increased every 2 weeks according to clinical response."

RELATED MARKETING APPLICATIONS OF SPONSOR:

NDA 9-330, Lanoxin Injection
NDA 18-118, Lanoxicaps

NONCLINICAL DATA: None included. We are referred to NDA 9-330 for nonclinical pharmacology and toxicology data.

LABELING: Consistent with requirements of 21CFR201.57. Reflects the absence of animal carcinogenicity and reproduction studies.

EVALUATION: Lanoxin tablets are currently marketed (since 1934) by Burroughs Wellcome for use in heart failure, atrial fibrillation, atrial flutter and paroxysmal atrial tachycardia. With NDA 20-405, the sponsor seeks approval for the use of Lanoxin tablets in heart failure patients receiving angiotensin converting enzyme inhibitors and diuretics or diuretics alone. The new indication is supported by two company-sponsored double-blind, placebo-controlled studies. The subject submission also provides for three new tablet strengths, 0.0625 mg, 0.1875 mg and 0.375 mg. These, along with the currently marketed 0.25 mg and 0.5 mg tablets, will be formulated or reformulated to make ingredients of all tablets (excluding coloring agents) the same as in the marketed 0.125 mg tablet (requires removal of from the 0.25 and 0.5 mg tablet formulations). Because Lanoxin tablets were grandfathered for approval under the 1938 FD&C Act (no application was ever submitted), the efficacy supplement route was unavailable for obtaining new indication or new formulation approval. Thus, the need for an original NDA.

As indicated under "LABELING", there is no animal data on which to base an assessment of the carcinogenic or mutagenic potential of digoxin or its potential to adversely affect fertility and reproduction. New drug applications and abbreviated new drug applications for other digoxin products, including sponsor's Lanoxicaps, have been approved with this same deficiency (Lanoxicaps approved in 1982). Although sponsor should be encouraged to conduct carcinogenicity, mutagenicity and reproduction studies with digoxin, failure to do so should not affect approvability.

RECOMMENDATION: Approvable.

Charles A. Resnick, Ph.D.

cc:
Orig NDA 20-405
HFD 110
HFD 110/CSO
HFD 110/CAResnick
car/10-9-93
wp51:\Lanoxin.Rev

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20405

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

APR | 8 1997

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA: 20-405 (Amendment) SUBMISSION DATE: MARCH 20, 1997
LANOXIN® (Digoxin) Tablets (0.0625, 0.125, 0.1875, 0.375, 0.25, 0.5 mg)

GLAXO WELLCOME REVIEWER: Emmanuel O. Fadiran, Ph.D.

TYPE OF SUBMISSION: RESPONSE TO CHANGE IN DISSOLUTION SPECIFICATION

BACKGROUND

Lanoxin® (Digoxin) has been marketed by the sponsor since 1934 but there has been no approved NDA for digoxin tablet. The sponsor submitted an NDA which was reviewed by the Division (03/08/94) and for which an approvable letter was issued on October 26, 1994. The sponsor's response to the Agency's comment on proposed dissolution specification was reviewed (Biopharm review dated December 13, 1995) and an interim dissolution specification of Q= at 60 minutes was set pending the availability of dissolution stability data at 45 minutes. In a submission dated 9/26/96 the sponsor submitted the stability dissolution data at 45 minutes and other information and requested that the proposed specification in the original NDA be accepted and this submission was reviewed on 12/18/96 and an approval of Q= at 60 minutes was recommended. The sponsor has now requested to clarify the dissolution specification in the approval letter sent to them.

Meeting between Bob Wolters (HFD-110), Bob Rippere (HFD-354) and Emmanuel Fadiran (Biopharm Reviewer, HFD-860) on 4/10/97

This meeting was held to discuss the sponsor's request and the ongoing revision by the USP for the dissolution specification for digoxin. The sponsor's request was discussed along with the Pharmacopeial Forum in-process revision for the dissolution specification for digoxin tablets (attached). The following decisions were made at the meeting:

(I) The 15 minutes test (test c) should be dropped (no need for "superdig" test)

(ii) The dissolution specification should be

Q= at 60 minutes and quantity of digoxin tablet dissolved in 60 minutes from each tablet must not be less than of the labeled strength at level 1 (number of tablets tested=6)

Average of digoxin dissolved in 60 minutes for a total of 12 tablets is not less than of the labeled strength and quantity of digoxin dissolved in 60 minutes from each tablet is not less than of the labeled strength at level 2 (number of tablets tested=12).

COMMENTS TO BE SENT TO THE FIRM:

(I) The 15 minutes test (test c) should be dropped.

(ii) The dissolution specification should be

Q= at 60 minutes and quantity of digoxin tablet dissolved in 60 minutes from each tablet must not be less than of the labeled strength at level 1 (number of tablets tested=6)

Average of digoxin dissolved in 60 minutes for a total of 12 tablets is not less than of the labeled strength and quantity of digoxin dissolved in 60 minutes from each tablet is not less than of the labeled strength at level 2 (number of tablets tested=12).

APPEARS THIS WAY
ON ORIGINAL

CONCLUSION:

The proposed dissolution specification for the Lanoxin® formulations should be as stated above. Please forward the above comments to the firm.

4/18/97

Emmanuel O. Fadiran, Ph.D.
Division of Pharmaceutical Evaluation I

FT Initialed by A. Parekh, Ph.D. 4/15/97

cc: NDA 20-405, HFD-110, HFD-860 (Fadiran), CDR (Attn: Barbara Muphy), Bob Wolters (HFD-110), Bob Rippere (HFD-354).

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CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA: 20-405 (Amendment) SUBMISSION DATE: JANUARY 27, 1995
LANOXIN® (Digoxin) Tablets (0.0625, 0.125, 0.1875, 0.375, 0.25, 0.5 mg)

BURROUGHS WELLCOME CO. REVIEWER: Emmanuel O. Fadiran, Ph.D.

TYPE OF SUBMISSION: RESPONSE TO CHANGE IN DISSOLUTION SPECIFICATION

BACKGROUND

Lanoxin® (Digoxin) has been marketed by the sponsor since 1934 but there is no approved NDA for digoxin tablet and this has created a chaotic situation with respect to generic applications. The sponsor submitted an NDA which was reviewed by the Division (03/08/94) and for which an approvable letter was issued on October 26, 1994. The firm has now responded to the proposed dissolution specification made in the review and considers the suggested specification inappropriate..

COMMENT

The proposed dissolution specification should be changed from Q = at 60 minutes to Q = at 45 minutes since the data provided on the clinical trial materials (Table 8, appendix) show that mean % dissolved > at 45 minutes for the three strengths of tablets used.

RESPONSE:

1. The proposed dissolution specification of Q= at 45 minutes is justified based on the following points:

(i). The dissolution specifications were set based on the data submitted to the NDA on the clinical trial lot of these new formulations of digoxin. The recent proposal of Q= at 60 minutes by the USP was based on the release properties of the old formulations of digoxin.

(ii) There will be no need for the specification of not more that dissolved in 15 minutes once this NDA is approved since any generic formulation has to be bioequivalent to the approved formulation (hence no incidence of "super dig" phenomenon).

2. Absence of 45-minute dissolution data on stability batches: The firm can obtain these data from samples that have been kept for their stability studies. Pending the availability of these data an interim dissolution specification of Q= at 60 minutes should be used for these formulations.

CONCLUSIONS:

The proposed interim dissolution specification for the Lanoxin® formulations is Q= at

60 minutes. The firm is requested to submit 45-minute dissolution data on the stability batches of the Lanoxin® formulations submitted to the NDA for the dissolution specification to be finalized.

12/12/95

Emmanuel O. Fadiran, Ph.D.
Division of Pharmaceutical Evaluation I

FT Initialed by A. Parekh, Ph.D. 12/13/95

cc: NDA 20-405, HFD-110, HFD-860 (Fadiran, Malinowski, Mehta), HFD-880 (Fleischer), HFD-870 (M. Chen), Chron, Drug, Review, FOI (HFD-19), HFD-340 (Vish), Dissolution.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

DEC 9 1994

NDA: 20-405 (Amendment) SUBMISSION DATE: JUNE 7, 1994
Priority: 7 S
LANOXIN® (Digoxin) Tablets (0.0625, 0.125, 0.1875, 0.375, 0.25, 0.5 mg)

BURROUGHS WELLCOME CO. REVIEWER: Emmanuel O. Fadiran, Ph.D.

TYPE OF SUBMISSION: RESPONSE TO REQUEST FOR INFORMATION

BACKGROUND

Lanoxin® (Digoxin) has been marketed by the sponsor since 1934 but there is no approved NDA for digoxin tablet and this has created a chaotic situation with respect to generic applications. The sponsor submitted an NDA which was reviewed by the Division (03/08/94) and the firm has now responded to one of the comments made in the review.

COMMENT 1(a)

The proposed dissolution specifications are different from those used for the old formulation but there has been no comparison made between the dissolution profiles of the old 0.25 and 0.5 mg tablet and the new 0.25 and 0.5 mg formulations. The firm should provide this information. This dissolution comparison will assure that the old formulations with stearic acid (on the market) and the new formulations without (to be marketed) have similar *in-vitro* release profiles.

RESPONSE:

The dissolution data for the 0.5 mg tablet with and without (Tables 1 and 2) submitted by the firm shows that both formulations have similar *in-vitro* release profiles (the formulation with stearic acid is 30 months old while the one without .... is 1 month old).The formulation with has a slower *in-vitro* dissolution when compared to the formulation without .... because of the long storage (this is why the sponsor has removed from the new formulations) but the impact of the minor in-vitro dissolution differences on the in vivo bioavailabilty may be minimal because more than of the old formulation is released after 60 minutes (the specification for the new formulation). Although there is no direct *in vivo* comparison of these formulation changes, a cross-study comparison (White *et al* (1971) Brit Med J, 1, 380-381, and Biostudy Q25:01-01 in NDA 20-405) shows similar plasma concentrations for the formulations with and without stearic acid.

CONCLUSION:

The firm has given a satisfactory response to Comment 1(a) in the review of NDA 20-405.

12/9/94

Emmanuel O. Fadiran, Ph.D.
Pharmacokinetics Evaluation Branch

FT Initialed by A Parekh, Ph.D. Ameeta Parekh 12/9/94

cc: NDA 20-405, HFD-110, HFD-426 (Fadiran, Fleischer), Chron, Drug, Review, FOI (HFD-19), HFD-340 (Vish).

Dissolution Data for LANOXIN® Tablets, 0.5 mg, With and Without

As requested, comparative dissolution data for tablets with and without using the USP dissolution method are provided below:

LANOXIN® Tablets, 0.5 mg
(without stearic acid)
Batch 0Y2773
% l.s. digoxin dissolved
(Tested 2/28/91; age at time of test: 1 month)

Tablet	Sampling Times (minutes)			
	15	30	45	60
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				

Average	72.8	85.1	90.5	92.7
%RSD	2.1	1.8	2.0	1.8
Minimum	70.6	82.2	87.8	90.0
Maximum	76.1	87.5	93.9	95.8
Range				

Dissolution conditions: 37°C, 500 mL, 0.1*N* HCl, USP Rotating Basket Apparatus

LANOXIN® Tablets, 0.5 mg
(with
Batch 2R1816[a]
% l.s. digoxin dissolved
(Tested 2/28/94; age at time of test: 30 months)

Tablet	Sampling Times (minutes)			
	15	30	45	60
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				

Average	67.5	79.1	83.5	86.5
%RSD	1.5	0.9	0.6	0.8
Minimum	66.4	77.6	82.6	85.3
Maximum	69.2	80.2	84.2	87.6
Range				

Batch 2R1816 has lower dissolution after 30 months of storage as expected based on previous experience with the 0.25 mg and 0.5 mg tablets. Reference is made to the Development Pharmaceutics, provided herein for your ease in review. The formulation containing : gives a decrease in tablet dissolution upon storage. This trend is not seen for the formulation without Dissolution stays consistent over the shelf-life.

NDA: 20-405
Priority: 5 S
LANOXIN® (Digoxin) Tablets (0.0625, 0.125, 0.1875, 0.375, 0.25, 0.5 mg)

SUBMISSION DATE: SEPT. 30, 1993

BURROUGHS WELLCOME CO.

REVIEWER: Emmanuel O. Fadiran, Ph.D.

TYPE OF SUBMISSION: NDA

BACKGROUND

Lanoxin® (Digoxin) has been marketed by the sponsor since 1934 but there is no approved NDA for digoxin tablet and this has created a chaotic situation with respect to generic applications. Presently the procedure for obtaining permission to market generic digoxin tablet involves a batch certification process on the basis of dissolution. In order to allow ANDAs to be accepted for generic digoxin tablet via comparison to an innovator product, the sponsor has submitted an NDA for this product. Lanoxin® Tablet is currently marketed in three strengths (0.125, 0.25, and 0.5 mg). The currently marketed 0.25 and 0.5 mg tablets contain ... as an excipient while the 0.125 mg is without The sponsor plans to remove the formulations with from the market and make all formulations without due to better dissolution performance with aging without The firm also intends to market additional tablet strengths of 0.0625, 0.1875, 0.375 mg. In a meeting held on 12/5/90 between the sponsor and the Agency it was agreed that the sponsor would cross reference the data base submitted to the Lanoxicaps NDA and that a bioequivalence study would be carried out to compare the new formulations (0.0625 mg , 0.5 mg) of Lanoxin® tablet (without with the existing 0.125 mg tablet and the marketed elixir.

SYNOPSIS

The sponsor has adequately reviewed the literature on the human pharmacokinetics of digoxin including studies on renal impairment and drug interaction. The firm has proposed an in-vitro dissolution method and specifications (S_{1a} - Q = at 60 minutes, S_{1b} - Q = at 15 minutes; S_{2a} - Q = at 60 minutes, S_{2b} - Q = at 15 minutes; see Appendix page 22 for more details); all the three tablet strengths used for the biostudy met these specifications. An open, four-period, four-treatment, cross-over, randomized multiple-dose study was carried out to compare the steady state bioavailabilty of the new formulations of Lanoxin® tablets (0.0625 mg and 0.5 mg; without) to the currently marketed 0.125 mg Lanoxin Tablet (also without and the bioavailability of digoxin from all the three tablet

formulations to the currently marketed Lanoxin® Pediatric Elixir. The analysis of the data from the study shows that the three tablet formulations are bioequivalent but the three tablet formulations are not bioequivalent to the elixir when administered in equal doses.
The labeling is deficient and the firm has been advised to up-date it.

STUDY SUMMARY

CONCLUSION

The sponsor has done an extensive review of the literature on the pharmacokinetics of digoxin in humans. The bioequivalence study undertaken by the sponsor shows that the two new formulations of Lanoxin® Tablets (0.0625 mg and 0.5 mg, without ; are bioequivalent to the marketed 0.125 mg Lanoxin® Tablet but the three tablet formulations are bioinequivalent to the Lanoxin® Pediatric Elixir. The dissolution method is acceptable but the specification should be changed to Q = at 45 minutes. The labeling is deficient.

COMMENTS TO BE SENT TO THE FIRM

1. DISSOLUTION:

a. The proposed dissolution specifications are different from those used for the old formulation but there has been no comparison made between the dissolution profiles of the old 0.25 and 0.5 mg tablet and the new 0.25 and 0.5 mg formulations. The firm should provide this information. This dissolution comparison will assure that the old formulations with (on the market) and the new formulations without (to be marketed) have similar in-vitro release profiles.

b. The dissolution specification proposed by the firm should be changed from Q = at 60 minutes to Q = at 45 minutes since the data provided by the firm on the clinical trial materials (Table 8, appendix) shows that mean % dissolved > at 45 minutes for the three strengths of tablets used.

c. Request for a waiver for an in-vivo bioavailability study: The Biopharmaceutics Section of the NDA did not contain any dissolution data on the intermediate strengths (0.1875, 0.25, 0.375 mg) but this information was available in the Chemistry Section of the NDA (Table 8b). Since these three tablet strengths have similar composition as the strengths used for the biostudy and the dissolution were comparable to the strengths and the lots used in the biostudy (page 23b), a request for a waiver for an in-vivo bioavailabilty study could be granted.

2. LABELING: The pharmacokinetics section of the labeling is deficient and does not conform to the current regulations on labeling for prescription drugs (CFR 201.57) and the digoxin labeling guidelines (CFR 310.500). The following changes are therefore to be made to the labeling :-

a. Absorption :

(i) Add the following statement
" Gastrointestinal absorption of digoxin is via a passive process with the primary site being the upper intestine "

(ii) The statements on food-effect should be modified as follows:
Change " When Lanoxin Tablets are taken after meals, the rate of absorption is slowed, but the total amount of digoxin absorbed is usually unchanged. When taken with meals high in bran fiber, however, the amount absorbed from an oral dose may be reduced "
to
"When Lanoxin Tablets are taken after meals, the rate of absorption is slowed as indicated by a reduction in the peak serum concentration (Cmax) but the total amount of digoxin absorbed as measured by the cumulative urinary excretion (CUE) is usually unchanged. When taken with meals high in bran fiber, however, the amount absorbed from oral dose may be reduced by a clinically insignificant amount".

b. Information on gender effects, elderly patients and in patients with liver impairment :
In a telephone conversation with Dr P. Edgar (the contact person for the firm) on 2/10/94 the firm was requested to search their in-house data base on digoxin for these information which are not included in the present labeling. The firm agreed to carry out the search and provide any information found. These information should be appropriately included in the labeling if they are available. If not available, the labeling state so.

RECOMMENDATION:
The Division of Biopharmaceutics recommends that the sponsor's NDA 20-405 be accepted for meeting the Biopharmaceutics requirements provided comments 1 and 2 above are addressed satisfactorily by the sponsor. Please convey this to the sponsor.
Comment 1b should also be forwarded to the chemist - HFD 110.

3/3/94
Emmanuel O. Fadiran, Ph.D.
Pharmacokinetics Evaluation Branch

FT Initialed by A Parekh, Ph.D. Ameeta Parekh 3/4/94

cc: NDA 20-405, HFD-110, HFD-426 (Fadiran, Fleischer), Chron, Drug, Review, FOI (HFD-19), HFD-340 (Vish), F.

APPENDIX

LITERATURE REVIEW: Tables 1 - 4 show the summary of the literature search on the pharmacokinetics of digoxin in humans.

COMPOSITION OF THE FORMULATIONS: Tables 5 and 6 show the compositions of the tablet formulations and the elixir formulation respectively.

DISSOLUTION: Table 7 shows the proposed product dissolution method and specification for the tablet formulations while Table 8 shows the results of dissolution testing on the three LANOXIN® tablet formulations while Table 8b shows the dissolution data from the Chemistry Section of the NDA.

LABELING: The pharmacokinetic section of the labeling is deficient and the firm has been advised to up-date it (see comment 2 above). A copy of the labeling is attached.

BIOEQUIVALENCE STUDY

CLINICAL STUDY NUMBER: Q25:01-01

INVESTIGATOR AND LOCATION:

STUDY PERIOD: April 6, 1991 - June 16, 1991.

OBJECTIVE: To compare at steady state (i) the bioavailability of the 0.5 mg Lanoxin® Tablets (without stearic acid) and the new strength of 0.0625 mg Lannoxin® Tablets to the currently marketed 0.125 mg Lanoxin® Tablets and (ii) the bioavailabilty of digoxin from all three tablet formulations to that from the currently marketed Lanoxin® Elixir Pediatric in healthy male volunteers following the same daily digoxin dose (0.5 mg/day).

TREATMENTS:

A = one 0.5 mg Lanoxin® Tablet, Formulation No. ANA-04A1, Batch No OY2773 (Batch size = _, _,_ tablets), Manufacturing Date - Feb 1, 1991, administered once daily for 14 days.

B = four currently marketed 0.125 mg Lanoxin® Tablets, Formulation No AMW-03A2, Batch No OY2775 (Batch size = tablets), Manufacturing Date - Dec 19,1990, administered once daily for 14 days.

C = eight 0.0625 mg Lanoxin® Tablets, Formulation No AMU-01B1, Batch No OZ2791 (Batch size = tablets), Manufacturing Date - Feb 28,1991, administered once daily for 14 days.

D = one 10 ml-dose of Lanoxin® Elixir Pediatric (0.05 mg/ml), Formulation No AMS-02B1, (Batch size = bottles), Manufacturing Date - not specified, administered once daily for 14 days.

STUDY DESIGN: Randomized, open, four-period, four-treatment, cross-over study with 28 healthy male volunteers. Subjects entered a 56-day treatment phase which included four consecutive 14-day dosing periods during which they received each of the four treatments above in each dosing period. A wash out period was not required because the design required dosing to steady state. Subjects were fasted 8 hours prior to dosing during the outpatient portions (Days 1-13, Day 16-27, Days 30-41, and Days 44 -55) and during the inpatient portions (Days 13-15, Days 27-29, Days 41-42, and Days 55-57) and received treatment at 0700 hrs on each day. Blood samples were collected prior to dosing on the two previous days and on the last day of each dosing period (to determine the Cmin) and at 15, 30, 45, 60, 75, 90 minutes , and 2, 3, 4, 6, 8, 12, and 24 hours after the administration of the last dose of each dosing period.

ASSAY:

DATA ANALYSIS: AUC, Cmax and Tmax were calculated. Statistical analysis were carried out using SAS software package (General Linear Models Procedure).

RESULTS: Tables 9-13 summarize the data obtained from the study while Figure 1 shows the mean serum digoxin concentration-time curves for all the volunteers for the four treatments. The analysis of the results of the study shows that the three tablet formulations are bioequivalent but the three tablet formulations are not bioequivalent to the elixir when administered in equal doses.

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Table 1 Digoxin Absolute Bioavailability Data by Route of Administration

Study Design	Dose (mg)	Formulation	N (volunteers)	CUE[a] (6 days)	Absolute Bioavailability (based on CUE)	Reference
Single-dose, incomplete block	0.4	tablets[b]	16	199 µg		Doherty, 1984
		oral solution	16	211 µg		
		iv infusion (1 hr)	15	256 µg		
Single-dose, incomplete block	0.4	tablets[b]	6	209 µg		Binnion, 1976
		oral solution	6	239 µg		
		iv infusion (1 hr)	6	279 µg		
Single-dose, crossover	0.4	tablets[b]	6	205.9 µg		Marcus, 1976
		oral solution	6	204.1 µg		
		iv infusion (1 hr)	6	240.5 µg		
Single-dose, crossover	0.75	tablets	8	0.31 mg		Greenblatt, 1973
		oral solution	8	0.37 mg		
		intramuscular injection	8	0.47 mg		
		iv infusion (1 hr)	8	0.57 mg		

[a]CUE = Cumulative Urinary Excretion

[b]Administered as two 0.2 mg tablets manufactured by Burroughs Wellcome Co. for clinical investigation.

[c]The Binnion and Marcus investigations were parts of the Doherty study.

Doherty JE, Marcus FI, Binnion PF. A multicenter evaluation of the absolute bioavailabilty of digoxin dosage forms. Curr Ther Res 1984; 35:301-6.

Binnion PF. A comparison of the bioavailabilty of digoxin in capsule, tablet, and solution taken orally with intravenous digoxin. J Clin Pharmacol 1976; 16:461-7.

Marcus FI, Dickerson J, Pippin S, Stafford M, Bressler R. Digoxin bioavailabilty: formulations and rates of infusion. Cli Pharmacol Ther 1976; 20:253-9.

Greenblatt DJ, Duhme DW, Koch-Weser J, Smith TW. Evaluation of digoxin bioavailabilty in single-dose studies. N Engl J Med 1973; 289:651-4.

Table 4 Effects of Food on Digoxin Pharmacokinetics

Meal Contents	Study Design	Dose (mg)	Treatments	N[a]	CUE[b]	Results/Conclusions	Referen
Usual breakfast	Single-dose, crossover	0.25	tablet, fasting tablet, immediately after usual breakfast	3 3	39% of dose 38% of dose	Rate of absorption is higher when tablets taken in the fasted state. Extent of absorption appears to be similar based on CUE.	Sanchez, 19
Standard breakfast (egg, cereal, milk, bread, juice or coffee)	Single-dose, crossover	0.75	tablets, fasting tablets, 30 minutes after a standard breakfast	8 8	0.31 mg (41% of dose) 0.27 mg (36% of dose)	Postprandial administration does not alter CUE but may alter rate of absorption.	Greenblatt,
Standard breakfast (2 cupfuls of Cornflakes, 150ml of milk, 1 fried egg, 2 slices of fried bacon, 1 slice of toast with butter, 150ml of coffee)	Single-dose, crossover	1.0	tablets, fasting tablets, immediately after a standard breakfast tablets, 90 minutes after a standard breakfast	6 6 6	504.8 μg (50.5% of dose) 544.7 μg (54.5% of dose) 484.0 μg (48.4% of dose)	Food taken prior to dosing does not affect the amount of digoxin absorbed. Rate of absorption is reduced in the postprandial state.	Johnson, 19
"Light" or "Substancial" based on the amount of food eaten	Multiple-dose, crossover	Maintenance therapy	daily dose 30 minutes before breakfast for two weeks daily dose 30 minutes after breakfast for two weeks	21 outpatients 21 outpatients	Not reported	No significant difference in plasma concentration when therapy taken after food.	White, 1971
Meals containing 0.75 g of crude fiber or 5 g of crude fiber	Single-dose, crossover	0.75	orally, fasting orally with a meal containing 0.75 g crude fiber (normal fiber) orally with a meal containing 5.0 g crude fiber (high fiber)	12 12 12	40.5% of dose 41.2% of dose 33.0% of dose	High amounts of fiber reduce digoxin bioavailability	Brown, 1977

[a] Volunteers unless otherwise stated

[b] Based on 5 days cumulative urinary excretions (CUE) in the study by Sanchez, 6 days in the study by Greenblatt, 10 days in the study by Johnson, and 6 days in study by Brown

Sanchez N, Sheiner LB, Halkin H, Melmon KL. Pharmacokinetics of digoxin: interpreting bioavailabilty. Br Med J 1973; 4:132-4.

Greenblatt DJ, Duhme DW, Koch-Weser J, Smith TW. Bioavailabilty of digoxin tablets and elixir in the fasting and postprandial states. Clin Pharmacol Ther 1974; 16:444-8.

Johnson BF, O'Grady J, Sabey GA, Bye C. Effect of a standard breakfast on digoxin in normal subjects. Clin Pharmacol Ther 1978; 23:315-9.

White RJ, Chamberlain DA, Howard M, Smith TW. Plasma concentrations of digoxin after oral administration in the fasting and postprandial state. Br Med J 1971; 1:380-1.

Brown DD, Juhl RP, Warner SL. Decreased bioavailabilty of digoxin produced by dietary fiber and cholestyramine [abstract]. Am J Cardiol 1977; 39:297.

Table 3. Drug Interactions Which Affect Digoxin Pharmacokinetics

Drugs Which Lower Bioavailability	Study Design	Paradigm	Study Findings	Representative References
Neomycin	Crossover, single-dose (n = 24 volunteers) Crossover, steady-state (n = 5 volunteers)	Either 0.1, 1, or 3 g neomycin either 3 or 6 hours before, or with, digoxin 0.5 mg. 0.25 mg digoxin daily alone and with 2 g neomycin. 3 subjects took treatment with a meal.	Inhibits both the rate and extent of digoxin absorption. Decreases AUC (by 41 to 51%), 6-day urinary excretion (by 42%)(single-dose portion), and steady-state serum digoxin concentration (by 28%). Effect also seen when antibiotic is given 3 to 6 hours before the digoxin dose.	Lindenbaum, 1976
Antacids (aluminum hydroxide, magnesium hydroxide, and magnesium trisilicate) and Kaolin-pectin	Crossover, single-dose (n = 10 volunteers)	0.75 mg digoxin alone and with 60 ml each of 4% aluminium hydroxide, 8% magnesium hydroxide, magnesium trisilicate, and kaolin-pectin.	Antacids: Reduced AUC (by ~26% for aluminum hydroxide, ~25% for magnesium hydroxide, and ~38% for magnesium trisilicate). Reduced CUE[a] (by ~26% for aluminum hydroxide, ~36% for magnesium hydroxide, and ~29% magnesium trisilicate). Kaolin-pectin: Reduced AUC (by ~41%) and CUE (by ~42%).	Brown, 1976
Sulfasalazine	Crossover, single-dose (n = 10 volunteers)	0.5 mg digoxin alone and after 6 days pretreatment with sulfasalazine.	Lowers AUC (by 24%) and total urinary excretion (by 18%). Rate of absorption and T_{max} remain unchanged.	Juhl, 1976
Cholestyramine	Crossover, single-dose (n = 22 volunteers) (Conducted in two portions) Crossover, steady-state (n = 4 volunteers)	0.75 mg of digoxin alone and with cholestyramine; 4 g, 8 g, 8 g 8 hours before digoxin, and 8 g 8 hours after digoxin. 0.5 mg of digoxin only for 14 days and with cholestyramine; 4 g qd, 4 g qid, and 8 g bid 8 hours before and after digoxin.	Interferes with the absorption of oral digoxin. In single-dose portion, CUE reduced (by 17% [4 g cholestyramine] to 31% [8 g cholestyramine]). Temporal separation of the time of administration of digoxin from cholestyramine minimizes the interference. Mechanism is presumably related to physical binding of digoxin to the resin.	Brown, 1978

[a]CUE=cumulative urinary excretion

Lindenbaum JK, Maulitz RM, Butler VP Jr. Inhibition of digoxin absorption by neomycin. Gastroenterology 1976; 71:399-404.

Brown DD, Juhl RP. Decreased bioavailability of digoxin due to antacids and kaolin-pectin. N Engl J Med 1976; 295:1034-7.

Juhl RP, Summers RW, Guillory JK, Blaug SM, Cheng FH, Brown DD. Effect of sulfasalazine on digoxin bioavailabilty. Clin Pharmacol Ther 1976; 20:387-94.

Brown DD, Juhl RP, Warner SL. Decreased bioavailability of digoxin due to hypocholesterolemic interveytions. Circulation 1978; 58:164-172.

Table 3 (cont.) Drug Interactions Which Affect Digo[illegible] Pharmacokinetics

Drugs Which Lower Bioavailability	Study Design	Paradigm	Study Findings	Representative References
Anticancer agents: Cyclophosphamide, cytarabine, BCNU, melphalan, methotrexate, procarbazine and vincristine, in combination	Parallel, single-dose (n = 13 patients with neoplastic disease)	Digoxin administered within 3 days before, and within 5 days after, chemotherapy. Six patients received LANOXIN® Tablets, 0.5 mg, and 7 patients received LANOXICAPS®, 0.4 mg.	Significant reduction in AUC (54.4% and 85.1% of the value before chemotherapy when digoxin administered as LANOXIN Tablets and LANOXICAPS, respectively) after chemotherapy Reduced absorption possibly due to cancer treatment-induced damage to intestinal epithelium.	Bjornsson, 1986
Cyclophosphamide, vincristine, procarbazine, and cytarabine, in combination	Single-dose (n = 6 patients with malignant lymphoma) Steady-state (n = 12 patients)	0.8 mg β-acetyldigoxin before and after chemotherapy. 0.3 mg β-acetyldigoxin maintenance therapy before and after cytostatic drug therapy.	Reversible impairment of absorption. AUC reduced (by 20 to 30% in single-dose portion). Mean plasma concentration and daily excretion also reduced (both by 50% in steady-state portion).	Kuhlmann, 1982
Drugs Which Increase Bioavailability	**Study Design**	**Paradigm**	**Study Findings**	**Representative References**
Propantheline	Incomplete block, multiple-dose (n = 18 volunteers)	Each volunteer received 4 of 6 continuous treatments for 2 weeks each: 0.5 mg digoxin in tablet form alone and with 15 mg propantheline bromide qid or with 8 g cholestyramine; and 0.4 mg digoxin as LANOXICAPS alone and with 15 mg propantheline bromide qid or with 8 g cholestyramine.	Increase in AUC (by 24%). Enhances absorption by decreasing gastric motility.	Brown, 1985

Bjornsson TD, Huang AT, Roth P, Jacob DS, Christenson R. Effects of high-dose cancer chemotherapy on the absorption of digoxin in two different formulations. Clin Pharmacol Ther 1986; 39:25-8.

Kuhlmann J. Inhibition of digoxin absoption but not of digitoxin during cytostatic drug therapy. Arzneimittelforschung/Drug Res 1982; 32:698-704.

Brown DD, Schmid J, Long RA, Hull JH. A steady-state evaluation of the effects of propantheline bromide and cholestyramine on the bioavailability of digoxin when administered as tablets or capsules. J Clin Pharmacol 1985; 25:360-4.

Table 3. (cont.) Drug Interactions Which Affect Digoxin Pharmacokinetics

Drugs Which Increase Bioavailability	Study Design	Paradigm	Study Findings	Representative References
Propantheline (cont)	Steady-state (n = 13 elderly female patients on digoxin maintenance therapy)	15 mg propantheline tid for 10 days.	Increases steady-state serum digoxin concentration (by ~30%). Lengthens effective absorption time by decreasing gastrointestinal motility.	Manninen, 1973
	Single-dose, parallel (n = 8 volunteers)	0.5 mg digoxin in tablet form (4 volunteers) or liquid form (4 volunteers) alone and with 30 mg propantheline 30 minutes before digoxin administration.	No obvious change in absorption when digoxin administered in the liquid form. Suggests propantheline does not affect bioavailability by improving the efficacy of the absorption sites.	
Diphenoxylate with atropine	Crossover, single-dose (n = 10 volunteers)	0.75 mg digoxin alone and with Lomotil®, 2 tablets 4 hr before and 2 tablets with digoxin.	Increased urinary excretion (by ~20%) indicates increased absorption.	Brown, 1979
Drugs Which Increase Plasma/Serum Digoxin Concentrations	**Study Design**	**Paradigm**	**Study Findings**	**Representative References**
Quinidine	Multiple-dose, add-on (n = 27 patients)	17 patients were receiving digoxin for ventricular failure and 10 for atrial arrhythmias: quinidine therapy was begun for atrial arrhythmias in 13 patients and for ventricular arrhythmias in 14 patients.	Mean serum digoxin concentration increased (by ~130%). Rise in serum digoxin concentrations likely due to displacement of digoxin from tissue binding sites by quinidine.	Leahey, 1978
	Multiple-dose, add-on (n = 12 patients)	Patients receiving digoxin for at least 4 weeks. Loading dose of quinidine sulphate (0.6–0.8 g) followed by maintenance doses of 750 mg quinidine bisulphate bid.	Rise in plasma digoxin concentration (by ~88%).	Ejvinsson, 1978

Manninen V, Apajalahti A, Melin J, Karesoja M. Altered absorption of digoxin in patients given probantheline and metoclopramide. Lancet 1973; 1:398-400.

Brown DD, Juhl RP. Altered bioavailability of digoxin produced by gastrointestinal medications [abstract]. Clin Res 1979; 27:610A.

Leahey EB Jr, Reiffel JA, Drusin RE, Heissenbuttel RH, Lovejoy WP, Bigger JT Jr. Interaction between quinidine and digoxin. JAMA 1978; 240:533-4.

Ejvinsson G. Effect of quinidine on plasma concentrations of digoxin. Br Med J 1978; 1:279-80.

Table 3. (cont.) Drug Interactions Which Affect Digoxin Pharmacokinetics

Drugs Which Increase Plasma/Serum Digoxin Concentrations	Study Design	Paradigm	Study Findings	Representative References
Quinidine (cont.)	Multiple-dose, crossover (n = 6 volunteers including one individual with pancreatic carcinoma, one with multiple sclerosis and psychiatric history, and one with tuberculosis)	Day 1: 1.0 mg digoxin i.v.; Day 5: 200 mg quinidine sulfate every 6 hr; Day 8: 0.75 mg digoxin i.v. (Subject 2 received 1.0 mg) with continued quinidine sulfate administration.	Reduction in total body clearance (by 35%) and reduction in renal clearance (by 30%) without a change in creatinine clearance suggests no change in GFR. Reduction in renal clearance may result from inhibition of renal secretion.	Hager, 1979
	Multiple-dose, add-on (n = 10 patients with chronic atrial fibrillation on digoxin maintenance therapy, scheduled for cardioversion)	Following 3 or more weeks on warfarin therapy, patients received loading dose of quinidine sulphate (0.1 g/10 kg body weight) followed by 600 mg quinidine sulphate bid. (Dosage of concomitant medications remained unchanged.)	Steady-state plasma concentration of digoxin increased by more than twofold. Renal digoxin clearance decreased (by 55%) with no change in GFR or total renal blood flow. Most probable explanation of reduction of renal clearance is inhibition by quinidine of tubular secretion of digoxin.	Schenck-Gustaffson, 1982
	Multiple-dose, crossover (n = 6 volunteers)	3 medication periods separated by 2-week washout periods. Period 1: after saturation with 1 mg digoxin i.v., subjects received 7-day medication of 0.4 mg β-acetyldigoxin per day; Period 2: 0.6 mg quinidine bid orally for 7 days; Period 3: 7-day medication of digoxin and quinidine as in Periods 1 and 2.	Steady-state serum digoxin concentrations increased (by 200%) due to a decrease (by ~48%) in renal clearance. GFR unchanged suggesting that quinidine inhibits renal tubular secretion of digoxin. Volume of distribution decreased (by 34%) due possibly to a decreased affinity of digoxin for cardiac receptor.	Rameis, 1985

Hager WD, Fenster P, Mayersohn M, Perrier D, Graves P, Marcus FI, et al . Digoxin-quinine interaction: pharmacokinetic evaluation. N Engl J Med 1979; 300:1238-41.

Schenck-Gustafsson k, Juhlin-Dannefelt A, Dahlquist R. Renal function and digoxin clearance during quinidine therapy. Clin Physiol 1982; 2:401-8.

Rameis H. Quinidine-digoxin interaction: are the pharmacokinetics of both drugs altered? Int J Pharmacol Toxicol 1985; 23:145-153.

Table 3. (cont.) Drug Interactions Which Affect Digoxi. , armacokinetics

Drugs Which Increase Plasma/Serum Digoxin Concentrations	Study Design	Paradigm	Study Findings	Representative References
Quinine	Single-dose, two-way crossover (n = 4 volunteers; 1 patient concomitantly being treated for pulmonary tuberculosis with isoniazid, erythromycin, streptomycin, rifampin, and ethionamide; and 1 patient with multiple sclerosis also receiving chlorpromazine and lithium carbonate).	Treatment period 1: 1.0 mg digoxin i.v. over 10 min; Treatment period 2: 200 mg quinine sulfate every 8 hr for 4 days prior to and after i.v. administration of 1.0 mg digoxin over 10 min.	Digoxin total body clearance reduced (by 26%). Digoxin elimination half-life lengthened reflecting a decrease (by 32%) in digoxin elimination rate constant. Renal excretion increased (by 23%) due to a decrease in nonrenal digoxin clearance (by 55%).	Wandell, 1980
	Multiple-dose, two-way crossover (n = 7 healthy volunteers)	Single oral loading dose of 1.0 mg digoxin followed by oral maintenance dosing of 0.1875 mg bid for a total of 14 days. Oral coadministration of quinine sulphate 250 mg qd and 0.1875 mg digoxin bid for 7 days followed by oral coadministration of quinine sulphate 250 mg tid for one week.	Plasma digoxin concentrations increased (by 25% and 44%, respectively, for the low- and high-dose of quinine). Urinary recovery of digoxin increased (by ~ 18% and ~ 32%, respectively, for the low- and high-dose of quinine). Possibly due to impairments of extrarenal elimination routes of digoxin.	Pedersen, 1985
	Multiple-dose, add-on (n = 4 healthy volunteers)	During steady-state therapy with oral digoxin (0.25 mg qd), 300 mg quinine sulphate qid were administered for four days.	Plasma digoxin concentration increased (by ~ 63% and 75% on day 1 and day 4, respectively). Renal digoxin clearance decreased (by ~ 20% on day 4)	Aronson, 1981
	Multiple-dose, add-on (n = 17 patients)	During steady-state therapy with oral digoxin, quinine sulphate (750 mg qd for 7 days) was added to the dosage regimen.	Serum digoxin concentration was not significantly increased after one week of coadministration of quinine.	Doering, 1981

Wandell M, Powell JR, Hager WD, Fenster PE, Graves PE, Conrad KA et al . Effect of quinine on digoxin kinetics. Clin Pharmacol Ther 1980; 28:425-30.

Pederson KE, Madsen JL, Kligaard NA, Kjoer K, Hvidt S. Effect of quinine on plasma digoxin concentration and renal digoxin clearance. Acta Med Scand 1985; 218:229-32.

Aronson JK, Carver JG. Interaction of digoxin with quinine [letter]. Lancet 1981; 1:1418.

Doering W. Is there a clinically relevant interaction between quinine and digoxin in human beings [letter]. Am J Cardiol 1981; 48:975.

Table ... (cont.) Drug Interactions Which Affect Digoxin Pharmacokinetics

Drugs Which Increase Plasma/Serum Digoxin Concentrations	Study Design	Paradigm	Study Findings	Representative References
Verapamil	Multiple-dose (n = 49 patients on maintenance therapy)	250 mg of verapamil per day in 3 divided doses for 2 weeks. In 26 patients, verapamil stopped and daily maintenance doses of digoxin were doubled. Two weeks later, verapamil started again in 5 patients.	Increase in serum digoxin concentrations (by ~72%) and decrease in renal digoxin clearance (by ~53%). Degree of increase in serum digoxin concentrations is proportional to the dose of verapamil. Verapamil decreases the renal digoxin clearance without affecting creatinine clearance suggesting verapamil decreases tubular secretion of digoxin.	Klein, 1982
	Crossover, single-dose (n = 8 volunteers)	1 mg digoxin i.v. (Subject #6 received 0.75 mg) and 0.75 mg i.v. (Subject #6 received 0.60 mg) after 10 days pretreatment with verapamil.	Decreased apparent central distribution volume (by ~23%) and reduced total body clearance (by ~34%) by impairing both renal and extrarenal clearance. Reduction in renal clearance may be due to inhibition of tubular secretion.	Pedersen, 1981
Amiodarone	Multiple-dose (n = 5 patients)	0.25 mg digoxin from day 0 to day 7 with 600 mg oral amiodarone administered from days 1 to 7.	Urine digoxin concentration increased (by ~95% on the 7th consecutive day of amiodarone dosing) and plasma digoxin concentrations increased (by ~102% on the 7th consecutive day of amiodarone dosing). These increases, along with the lack of toxicity, suggest amiodarone may displace digoxin from its tissue-binding sites.	Douste-Blazy, 1984
	Multiple-dose (n = 7 patients on maintenance therapy)	200 mg amiodarone tid on days 3-7.	Plasma digoxin concentration increased progressively (by an average of 69%). Amiodarone avidly tissue bound; therefore, it may displace tissue-bound digoxin and interfere with excretion.	Moysey, 1981
Propafenone	Crossover, multiple-dose (n = 12 volunteers)	0.125 mg digoxin tid. Administration of placebo, quinidine bisulfate (250 mg), and propafenone(150 mg) for 2 weeks with digoxin at steady state.	Propafenone increased plasma digoxin concentration (by ~37%) and decreased renal digoxin clearance (by ~17%).	Belz, 1983

Klein HO, Lang R, Weiss E, DiSegni E, Libhaber C, Guerrero J, et al. The influence of verapamil on serumdigoxin concentration. Circulation 1982; 65:998-1003.

Pedersen KE, Dorph-Pedersen A, Hvidt S, Klitgaard NA, Nielsen-Kudsk F. Digoxin-verapamil interaction. Clin Pharmacol Ther 1981; 30:311-6.

Doutste-Blazy P, Montastruc JL, Bonnet B, Auriol P, Conte D, Bernadet P. Influence of amiodarone on plasma and urine digoxin concentrations [letter]. Lancet 1984; 1:905.

Moysey JO, Jaggarao NSV, Grundy EN, Chamberlain DA. Amiodarone increases plasma digoxin concentrations. Br Med J 1981; 282:272.

Belz GG, Doering W, Munkes R, Matthews J. Interaction between digoxin and calcium antagonists and antiarrhythmic drugs. Clin Pharmacol Ther 1983; 33:

Table 3. (cont.) Drug Interactions Which Affect Digoxin Pharmacokinetics

Drugs Which Increase Plasma/Serum Digoxin Concentrations	Study Design	Paradigm	Study Findings	Representative References
Spironolactone	Multiple-dose, add-on (n = 13 hospitalized patients with congestive heart failure receiving 0.25 to 0.5 mg digoxin qd, 40 to 160 mg furosemide qd, and supplemental potassium for at least one month)	Spironolactone, 100 mg qd, was added to the regimen of 9 of the 13 patients.	Plasma digoxin concentrations rose (by ~25%) during treatment with spironolactone, suggesting an inhibition of tubular secretion of digoxin in the distal segment of the renal tubules.	Steiness, 1974
	Two-period, two-treatment (n = 4 hospitalized patients with arteriosclerotic heart disease and 4 healthy volunteers)	Period 1: single i.v. dose of 0.75 mg digoxin (control); Period 2: after 5 days pretreatment with 100 mg spironolactone bid, single i.v. dose of 0.75 mg digoxin administered with continued administration of spironolactone.	Total plasma clearance of digoxin was reduced during spironolactone treatment (median reduction = 26%).	Waldorff, 1978
	Four-period, four-treatment, crossover (n = 6 normal subjects)	Administration of the following four treatments separated by at least 3 weeks: (1) single i.v. dose of 1.0 mg digoxin (control); (2) 200 mg quinidine every 6 hours for 3 days before and 5 days after the administration of 1.0 mg digoxin i.v.; (3) 50 mg spironolactone every 6 hours for three days before and 5 days after the administration of 1.0 mg digoxin i.v.; and (4) same doses and schedule for administration of both quinidine and spironolactone with 1.0 mg digoxin i.v. administered after 3 days.	Spironolactone alone decreased systemic, renal, and nonrenal clearances of digoxin (by 31%, 18%, and 44%, respectively).	Fenster, 1984

Steiness E. Renal tubular secretion of digoxin. Circulation 1974; 50:103-7.

Waldorff S, Andersen JD, Heeboll-Nielsen N, Nielsen OG, Moltke E, Sorensen U, et al. Spironolactone-induced changes in digoxin kinetics. Clin Pharmacol Ther 1978; 24:162-7.

Fenster PE, Hager WD, Goodman MM. Digoxin-quinine-spironolactone interaction. Clin Pharmacol Ther 1984; 36:70-3.

Table 3. (cont.) Drug Interactions Which Affect Digoxin Pharmacokinetics

Drugs Which Increase Plasma/Serum Digoxin Concentrations	Study Design	Paradigm	Study Findings	Representative References
Tetracycline hydrochloride	Multiple-dose (n = 1 volunteer)	0.5 mg digoxin for 17 days, 0.5 mg digoxin and 500 mg tetracycline hydrochloride for 5 more days, and 0.5 mg digoxin for an additional week after antibiotic therapy.	Tetracycline increased serum digoxin concentration (by ~43%).	Lindenbaum, 1981
Erythromycin	Case Report		71-year-old female developed elevation of digoxin concentration (steady-state concentration of 1.4 to 1.7 ng/ml increased to 2.6 ng/ml) associated with ECG and gastrointestinal toxicity four days after receiving 1 g erythromycin. Toxicity did not recur when the same dosage was resumed one month later.	Friedman, 1982
	Multiple-dose (n = 2 volunteers)	0.5 mg digoxin for 10 or 17 days, 0.5 mg digoxin and 1 to 2 g erythromycin for 5 more days, and 0.5 mg digoxin for an additional week after antibiotic therapy.	Serum digoxin concentration increased (by ~75 and ~116%).	Lindenbaum, 1981

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Lindenbaum J, Rund DG, Butler VP Jr, Tse-Eng D, Saha JR. Inactivation of digoxin by the gut flora: reversal by antibiotic therapy. N Engl J Med 1981; 305:789-94.

Friedman HS, Bonventre MV. Erythromycin-induced digoxin toxicity [letter]. Chest 1982; 82;202.

Lindenbaum J, Long R, Wenger T, Butler VP Jr, Rund DG. Urinary ecretion of reduced metabolites of digoxin. Am J Med 1981; 71:67-74.

Table 3. (cont.) Drug Interactions Which Affect Digoxin Pharmacokinetics

Drugs Which Decrease Plasma/Serum Digoxin Concentrations	Study Design	Paradigm	Study Findings	Representative References
Penicillamine	Single-dose, crossover (n = 10 patients in Group I, 13 in Group II, and 10 in Group III)	Patients stabilized on digoxin. Group I: 1 g oral penicillamine 2 hr after daily digoxin dose; Group II: 1 g oral penicillamine 16 hr after daily digoxin dose; Group III: 1 g oral penicillamine 2 hr after daily dose of digoxin administered i.v.	Serum digoxin concentrations decreased following both oral and i.v. digoxin dosing (by ~ 40% and ~65%, respectively, based on penicillamine administration 2 hr after digoxin and serum concentrations 6 hr after penicillamine administration). Serum digoxin concentration also reduced (by ~23 %) when penicillamine administered 16 hr after digoxin	Moezzi, 1978
Rifampin	Case Report		A 36-year-old female receiving dialysis three times a week developed heart failure and was treated with i.v. digoxin (administered at the end of the each dialysis session). Following reactivation of an old pulmonary tuberculosis lesion, patient was treated with rifampin 450 mg qd and isoniazid 200 mg qd on dialysis days and 100 mg on other days. A decrease in serum digoxin concentrations occurred despite increases in digoxin doses. Substitution of ethambutol 1,000 mg for rifampin resulted in observed increases in serum digoxin concentrations within 48 hours. Possible Explanation: Rifampin induced the metabolism of digoxin.	Novi, 1980

Moezzi B, Fatourechi V, Khozain R, Eslami B. The effect of penicillamine on serum digoxin levels. Jpn Heart J 1978; 19:366-70.

Novi C, Bissoli F, Simonati V, Volpini T, Baroli A, Vignati G. Rifampicin and digoxin: possible drug interaction in a dialysis patient [letter]. JAMA 1980; 244:2521-2.

Table 3. (cont.) Drug Interactions Which Affect Digoxin Pharmacokinetics

Drugs Which Decrease Plasma/Serum Digoxin Concentrations	Study Design	Paradigm	Study Findings	Representative References
Rifampin (cont.)	Two Case Reports		Report 1: A 47-year-old female with renal failure from systemic lupus erythematosus was on dialysis for four hours three times a week. Digoxin elixir, 0.08 mg/day, was administered to treat ischemic and hypertensive heart disease. Serum digoxin concentrations averaged 1.0 ng/ml. Rifampin, 300 mg/day, was started about three months later to treat the intractable infection of a polytetrafluoroethylene graft by *Staphylococcus aureus*. Serum digoxin concentrations fell to 0.2 to 0.3 ng/ml. Digoxin elixir doses were increased to 0.15 mg/day. After discontinuation of rifampin, the digoxin dose was reduced to 0.08 mg/day for five days and then increased to 0.15 mg/day which resulted in serum digoxin concentrations as high as 2.3 ng/ml. When the digoxin dose of 0.08 mg/day was restarted, serum digoxin concentrations leveled off to 0.8 to 1.3 ng/ml. Report 2: A 60-year-old man was on dialysis for five hours three times a week. Hypertensive ischemic heart disease associated with persistent atrial fibrillation was treated with digoxin with daily dosing alternating between 0.125 and 0.25 mg. The average serum digoxin concentration was 1.7 ng/ml. Rifampin, 600 mg qd, and isoniazid, 300 mg qd, were given to treat myobacterium tuberculosis. During rifampin therapy, the daily digoxin dose was 0.25 mg and the mean steady-state serum digoxin concentration was 1.6 ng/ml. Eighteen months after discontinuation of rifampin therapy, a daily digoxin dose of 0.125 mg resulted in a mean serum digoxin concentration of 2.0 ng/mL. Summary Finding: Serum digoxin concentrations might fall to ineffective concentrations with rifampin therapy and rise to potentially toxic concentrations when rifampin is discontinued.	Gault, 1984

Gault H, Longerich L, Dawe M, Fine A. Digoxin-difampin interaction. Clin Pharmacol Ther 1984; 35:750-4.

Table 3. (cont.) Drug Interactions Which Affect Digoxin Pharmacokinetics

Drugs Which Decrease Plasma/Serum Digoxin Concentrations	Study Design	Paradigm	Study Findings	Representative References
Rifampin (cont.)	Case Report		A 55-year-old female with a history of rheumatic fever and mitral valve replacement, atrial fibrillation, and exertional angina was diagnosed with *Staphylococcus epidermidis* endocarditis. The patient was receiving digoxin, furosemide, aspirin, isosorbide dinitrate, and potassium chloride. Following treatment with vancomycin and gentamicin, 600 mg rifampin qd was administered for additional antibiotic coverage. After four days of rifampin therapy, the serum digoxin concentration declined. After the digoxin dose was increased (from 0.25 mg/day to alternating between 0.25 and 0.375 mg every day), the serum digoxin concentration continued to decline to as low as 0.6 ng/ml. Rifampin therapy was discontinued and the digoxin dose was reduced to 0.25 mg/day. The serum digoxin concentration increased to as high as 2.6 ng/ml. Possible Mechanism: Rifampin increased the metabolism of digoxin producing lower serum digoxin concentrations.	Bussey, 1984

BusseyHI, Merritt GJ, Hill, EG. The influence of rifampicin on quinidine and digoxin. Arch Intern Med 1984; 144:1021-3.

Table 3 (cont.) Drug Interactions Which Affect Digoxin Pharmacokinetics

Drugs Which Decrease Plasma/Serum Digoxin Concentrations	Study Design	Paradigm	Study Findings	Representative References
Metoclopramide	Multiple-dose, add-on (n = 11 elderly female patients receiving digoxin maintenance therapy)	10 mg metoclopramide tid for 10 days	Steady-state serum digoxin concentrations decreased (by ~ 36%) during metoclopramide therapy. Serum digoxin concentrations returned to the initial concentrations after metoclopramide was discontinued. Possible Explanation: Metoclopramide shortens effective digoxin absorption time by increasing the rate of passage through the gastrointestinal tract.	Manninen, 1973
	Single-dose, crossover (n = 16 healthy male volunteers)	Treatment A: day 1, no metoclopramide; day 2, two 0.25-mg digoxin tablets with water alone. Treatment B: day 1, 10-mg metoclopramide tablet 30 min before meals and at bedtime; day 2, two 0.25-mg digoxin tablets and one 10-mg metoclopramide tablet 30 min before digoxin dosing and meals. Treatment C: day 1, no metoclopramide; day 2, two 0.2-mg digoxin capsules with water alone. Treatment D: day 1, 10-mg metoclopramide tablet 30 min before meals and at bedtime; day 2, two 0.2-mg digoxin capsules and one 10-mg metoclopramide tablet 30 min before digoxin dosing and meals.	Metoclopramide reduced mean digoxin absorption (by 23.5% and 18.0% as evaluated by AUC-24 and CUE-48, respectively) when digoxin was administered in the tablet form. When digoxin was administered in the form of a solution encapsulated in soft gelatin, metoclopramide did not have a significant effect on digoxin absorption.	Johnson, 1984

Manninen V, Apajalahti A, Melin J, Karesola M. Altered absoption of digoxin in patients given propantheline and metoclopramide. Lancet 1973; 1:398-400.

Johnson BF, Bustrack JA, Urbach DR, Hull JH, Marwaha R. Effect of metoclopramide on digoxin absorption from tablets and capsules. Cli Pharmacol Ther 1982; 36:724-30.

Table 4. Serum Digoxin Concentration Ranges in Patients by Disease State

Disease State	Patients (Number and Description)	Mean ± SD Concentration for Nontoxic Patients	Mean ± SD Concentration for Toxic Patients	Comments	Reference
Congestive heart failure, supraventricular tachyarrhythmia, or a combination	131 nontoxic patients 48 toxic patients	1.4 ± 0.7 ng/mL	3.7 ± 1.0 ng/mL	90% of patients without evidence of toxicity had concentrations of 2.0 ng/mL or less. 87% of the toxic group had concentrations above 2.0 ng/mL.	Smith, 1970
Congestive heart failure secondary to coronary atherosclerotic, valvular, hypertensive, or other heart disease	62 nontoxic patients 21 toxic patients	1.0 ± 0.5 ng/mL	2.3 ± 1.6 ng/mL		Beller, 1971
Not specified	10 patients taking 0.25 mg daily 11 patients taking 0.50 mg daily 18 patients with evidence of toxicity taking less than 0.25 mg daily	1.1 ± 0.3 ng/mL (range 0.8 to 1.6) 1.4 ± 0.4 ng/mL (range 0.9 to 2.4)	3.3 ± 1.5 ng/mL (range 2.1 to 8.7)		Smith, 1969
Congestive heart failure secondary to coronary, hypertensive, or valvular heart disease, cor pulmonale, myocardial disease, or other	100 consecutive patients with suspected digitalis-induced arrhythmias	1.00 ± 0.61 ng/mL (N = 76)	2.88 ± 1.89 ng/mL (N = 24)	Arrhythmias considered digitalis induced if they disappeared with the discontinuation of digitalis administration.	Bernabei, 1980

Smith TW, Haber E. Digoxin intoxication: the relationship of clinical presentation to serum digoxin concentration. J Clin Invest 1970; 49:2377-86.

Beller GA, Smith TW, Abelmann WH, Haber E, Hood WB Jr. Digitalis intoxication: a prospective clinical study with serum level correlations. N Engl J Med 1971; 284:989-97.

Smith TW, Butler VP, Haber E. Determination of therapeutic and toxicserum digoxin concentrations by radioimmunoassy. N Engl J Med 1969; 281:1212-6.

Bernabei R, Perna GP, Carosella L, DiNardo P, Cocchi A, Weisz AM, et al. Digoxin serum concentration measurement in patients with suspected digitalis-induced arrhythmias. J Cardiovasc Pharmacol 1980; 2:319-29.

Table 5. Composition of LANOXIN® Tablets

LANOXIN Product	0.50 mg tablet	0.375 mg tablet	0.25 mg tablet	0.1875 mg tablet	0.125 mg tablet	0.0625 mg tablet
Batch No. (if included in bioequivalence study)	0Y2773	NA	NA	NA	0Y2775	0Z2791
Formulation No. (if included in bioequivalence study)	ANA-04A1	NA	NA	NA	AMW-03A2	AMU-01B1
Composition (mg per tablet)						
Digoxin, USP (micronized)	0.50	0.375	0.25	0.1875	0.125	0.0625
D & C Yellow No. 10 Dye						
F D & C Yellow No. 6 Dye						
Lactose, NF						
Magnesium Stearate, NF						
Pregelatinized Starch, NF (corn)						
Starch, Potato, Dried						
Purified Water, USP[a]						
TOTAL (mg)						

[a]Removed during processing.
qs – quantity sufficient
NA – Not applicable. These tablets were not evaluated in the bioequivalence study.

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Table 6. Composition of LANOXIN® Elixir Pediatric

Batch No. used in bioequivalence study	0Y2776
Formulation No. used in bioequivalence study	AMS-02B1
Composition	
Digoxin, USP (crystalline)	0.00505%

APPEARS THIS WAY
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Table . Proposed Product Dissolution Method and Specification

Dissolution Method	
Dosage Form:	Tablets
Strength:	0.5, 0.375, 0.25, 0.1875, 0.125, and 0.0625 mg
Apparatus Type:	
Media:	
Volume:	
Speed Rotation:	
Sampling Time(s):	
Brief Description of Dissolution Analytical Method:	

Stage	Number tablets tested	Acceptance Criteria
S_{1a}	6	The average quantity of digoxin dissolved in 60 minutes is not less than of labeled strength. No tablet differs from the average by more than 5% of labeled strength. The quantity of digoxin dissolved in 60 minutes from each tablet may not be less than . of labeled strength.
S_{1b}	6[a]	If any tablet from the Stage S_{1a} is above labeled strength, then the quantity dissolved in 15 minutes for each tablet is not greater than of labeled strength.
S_{2a}	6	If any tablet from Stage S_{1a} differs from the average by more thar of labeled strength, then the average quantity of digoxin dissolved in 60 minutes for a total of 12 tablets is not less than of labeled strength. The quantity of digoxin dissolved in 60 minutes from each tablet may not be less than . of labeled strength.
S_{2b}	6[b]	If any tablet from the Stage S_{2a} is above labeled strength, then the quantity dissolved in 15 minutes for each tablet is not greater than labeled strength.

[a]The data for this stage may be from the six tablets from S_{1a} or from six additional tablets

[b]The data for this stage may be from the six tablets from S_{2a} or from six additional tablets

Table 8. Drug Product Dissolution Testing

Date of Test	Tablet Strength	Batch Number	Dissolution Apparatus	Media/ Temperature	Speed of Rotation	Collection Times (min)	Units Tested	Mean % Dissolved	CV	Range
3/11/91 and 3/14/91[a]	0.50 mg	0Y2773				15	12	72.8	2.1	
						30		85.1	1.8	
						45		90.5	2.0	
						60		92.7	1.8	
3/15/91 and 3/26/91[b]	0.125 mg	0Y2775				15	24	77.3	1.8	
						30		88.2	2.5	
						45		92.5	2.1	
						60		94.2	2.8	
3/20/91	0.0625 mg	0Z2791				15	12	76.4	3.4	
						30		86.5	2.3	
						45		90.1	2.4	
						60		92.1	2.8	

[a]One set of 6 tablets was analyzed on 3/11/91 and a second set of 6 tablets was analyzed on 3/14/91.

[b]Two sets of 6 tablets were analyzed on 3/15/91 and two sets of 6 tablets were analyzed on 3/26/91. A total of 24 tablets were analyzed.

Table 9. Individual Serum Digoxin Concentration Data (ng/mL)

Treatment A
(1 X 0.5 mg LANOXIN® Tablet)

Subject ID	Time (hr) 0.00	0.00	0.00	0.25	0.50	0.75	1.00	1.25	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00
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Mean	1.16	1.14	1.22	1.51	2.40	2.99	3.04	2.95	2.87	2.64	2.40	2.26	1.66	1.60	1.25	1.23
SD	0.28	0.25	0.23	0.41	0.76	0.81	0.71	0.63	0.54	0.40	0.39	0.38	0.32	0.35	0.27	0.29
%CV	24.22	21.65	18.84	26.79	31.57	26.99	23.34	21.28	18.76	15.30	16.12	16.61	19.34	22.15	21.55	23.54

Table 10. Individual Serum Digoxin Concentration Data (ng/mL), (cont'd)

Treatment B
(4 X 0.125 mg LANOXIN® Tablet)

Subject ID	Time (hr) 0.00	0.00	0.00	0.25	0.50	0.75	1.00	1.25	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00
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Mean	1.16	1.14	1.28	1.62	2.68	3.27	3.36	3.15	2.94	2.65	2.40	2.21	1.76	1.59	1.27	1.24
SD	0.24	0.27	0.22	0.45	0.74	0.76	0.83	0.74	0.53	0.38	0.39	0.33	0.31	0.34	0.27	0.31
% CV	20.75	23.73	17.63	27.64	27.56	23.22	24.81	23.46	17.89	14.41	16.24	14.90	17.56	21.31	21.46	24.94

Table 11. Individual Serum Digoxin Concentration Data (ng/mL), (cont'd)

Treatment C
(8 X 0.0625 mg LANOXIN® Tablet)

Subject ID	Time (hr) 0.00	0.00	0.00	0.25	0.50	0.75	1.00	1.25	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00
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Mean	1.12	1.13	1.24	1.60	2.51	3.20	3.36	3.29	3.04	2.75	2.54	2.40	1.73	1.59	1.30	1.17
SD	0.31	0.31	0.27	0.53	0.82	0.79	0.84	0.78	0.63	0.43	0.51	0.46	0.34	0.33	0.35	0.26
% CV	27.58	27.34	21.91	33.09	32.52	24.72	24.83	23.56	20.82	15.51	20.11	19.15	19.63	20.59	26.74	22.13

Table 12 - Individual Serum Digoxin Concentration Data (ng/mL), (cont'd)

Treatment D
(10 mL X 0.05 mg/mL LANOXIN® Elixir Pediatric)

Subject ID	Time (hr) 0.00	0.00	0.00	0.25	0.50	0.75	1.00	1.25	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24
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Mean	[illegible]	[illegible]	[illegible]	[illegible]	4.52	4.68	4.22	3.62	3.13	2.77	2.46	2.29	1.77	1.66	1.31	[illegible]
SD	0.29	0.32	0.30	1.09	1.07	0.97	0.90	0.80	0.66	0.56	0.50	0.44	0.36	0.35	0.33	[illegible]
% CV	23.43	26.08	21.98	38.27	23.75	20.77	21.30	22.08	20.95	20.35	20.21	19.10	20.36	21.15	24.90	24.0

Table 13. Lanoxin Tablet Bioequivalence Study (Q25-01-01)

Summary of ANOVA Results for the Natural Logarithmic Transformed Noncompartmental Pharmacokinetic Parameters at Steady State

Parameters	Mean(t)[a]	Mean(r)[b]	Mean(t) / Mean(r)	p-Value	90% Confidence[c] Interval	
					Lower	Upper
Treatment A (1 x 0.5 mg Tablet) vs Treatment B (4 x 0.125 mg Tablets)						
AUC (hr*ng/ml)	37.05	37.75	0.982	0.4329	0.94	1.02
Cmax (ng/ml)	3.33	3.52	0.947	0.0915	0.90	1.00
Cmin (ng/ml)	1.15	1.17	0.980	0.5273	0.93	1.03
Treatment C (8 x 0.0625 mg Tablet) vs Treatment B (4 x 0.125 mg Tablet)						
AUC (hr*ng/ml)	37.86	37.75	1.003	0.9013	0.96	1.04
Cmax (ng/ml)	3.52	3.52	1.000	0.9988	0.95	1.06
Cmin (ng/ml)	1.13	1.17	0.967	0.2855	0.92	1.02
Treatment A (1 x 0.5 mg Tablet) vs Treatment D (10 ml x 0.05 mg/ml Elixir)						
AUC (hr*ng/ml)	37.05	40.30	0.919	0.0006	0.88	0.96
Cmax (ng/ml)	3.33	4.90	0.680	0.0000	0.65	0.72
Cmin (ng/ml)	1.15	1.24	0.924	0.0139	0.88	0.97
Treatment B (4 x 0.125 mg Tablet) vs Treatment D (10 ml x 0.05 mg/ml Elixir)						
AUC (hr*ng/ml)	37.75	40.30	0.937	0.0068	0.90	0.97
Cmax (ng/ml)	3.52	4.90	0.718	0.0000	0.68	0.76
Cmin (ng/ml)	1.17	1.24	0.943	0.0636	0.90	0.99
Treatment C (8 x 0.0625 mg Tablet) vs Treatment D (10 ml x 0.05 mg/ml Elixir)						
AUC (hr*ng/ml)	37.86	40.30	0.939	0.0096	0.90	0.98
Cmax (ng/ml)	3.52	4.90	0.718	0.0000	0.68	0.76
Cmin (ng/ml)	1.13	1.24	0.912	0.0041	0.87	0.96

[a] Geometric means for the test treatment (n=28).
[b] Geometric means for the reference treatment (n=28).
[c] Two one-sided test procedure (Schuirmann DJ, *J. Pharmacokin. Biopharm.*, 15:667-680, 1987).

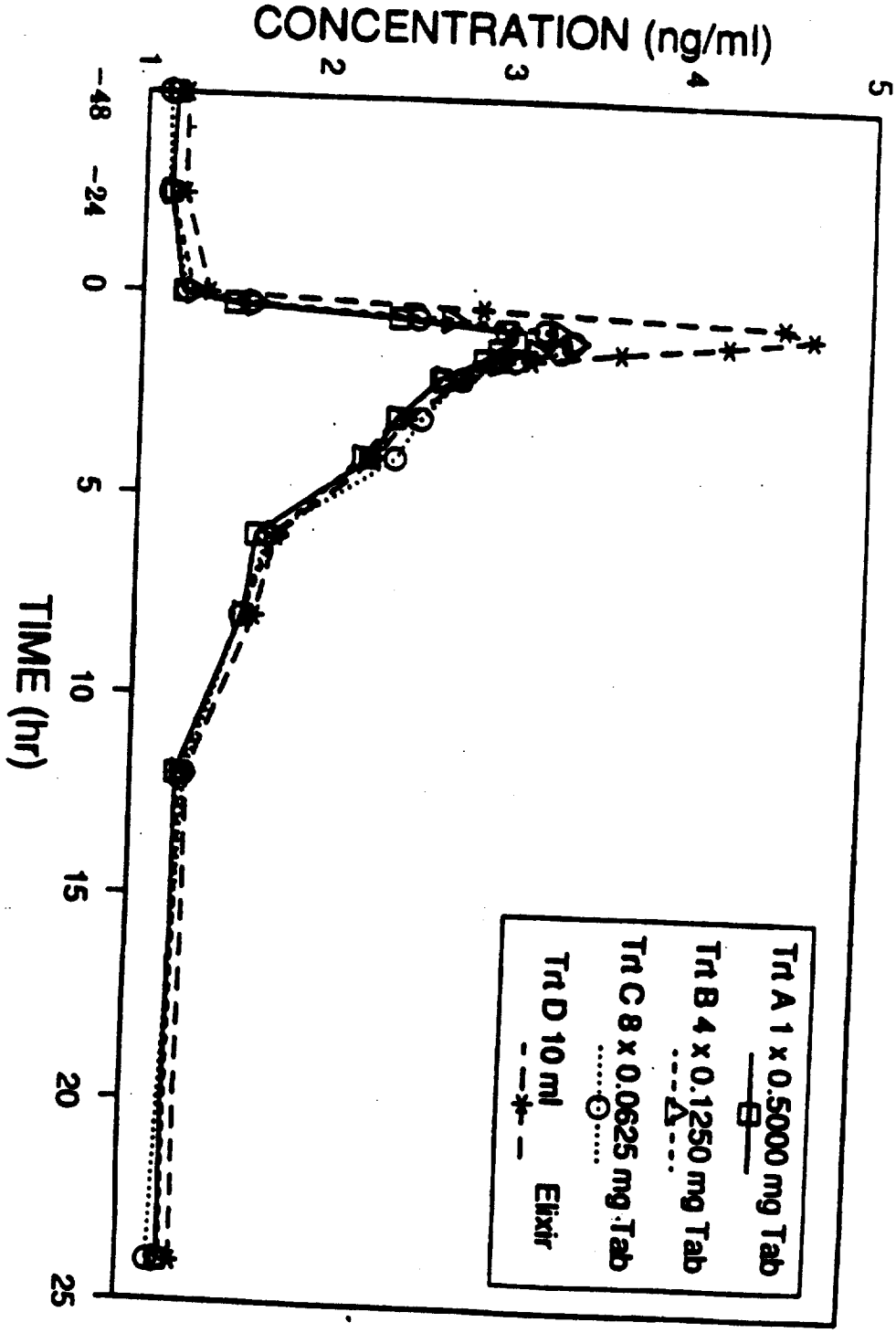

Figure 1. Mean Serum Digoxin Concentration vs. Time Profile

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