CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-648

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-648	
Submission Date	April 10, 2003 January 27, 2004
Drug Name	Digoxin
Tablet Strengths	Elixir (0.05 mg/ml)
Sponsor	Roxane Laboratories, Inc.
OCPB Reviewer	Venkatesh Atul Bhattaram Ph.D
OCPB Team Leaders	Joga Gobburu, Ph.D Patrick Marroum, Ph.D

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Executive Summary

Roxane Laboratories has submitted a 505(b)(2) New Drug Application for Digoxin Elixir 0.05 mg/mL (NDA 21648). Also, the sponsor is seeking approval for the use of digoxin in patients with less than 2 years of age for heart failure and atrial fibrillation. Digoxin (Lanoxin® tablets) is currently approved for heart failure and atrial fibrillation in adult and pediatrics (> 2 years).

Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the information submitted in NDA 21648. Based on the information provided by the sponsor the following are the OCPB recommendations:

1. The elixir formulation has been found to be bioequivalent to Lanoxin® tablets in the fasted and fed condition in healthy adult volunteers. In accordance with 505(b)(2), the Lanoxin® tablet labeling should be applied to the current elixir formulation.
2. The sponsor proposed a dosing scheme for pediatrics less than 2 years of age solely based on pharmacokinetics. However, the target pediatric population is not well defined and no reasoning has been provided by the sponsor why the target concentration in adults and pediatrics should be identical. Digoxin is a narrow therapeutic index drug with high unexplained variability. There does not seem to be enough basis to provide rational dosing recommendations for pediatrics < 2 years of age. The sponsor is encouraged to conduct a trial using relevant biomarkers in patients < 2 years of age and should make a case why these biomarkers are relevant. Also, prior to such a trial the sponsor should develop and validate a digoxin-specific assay method for use in neonates and infants.
3. OCPB reviewed the literature and the PDR to suggest an extensive list of potential drug-drug and drug-herbal product interactions. The proposed labeling changes should be adopted by the sponsor.

Venkatesh Atul Bhattaram, Ph.D
Division of Pharmaceutical Evaluation I
Primary Reviewer

The required OCPB briefing was held on February 11th, 2004. The attendees were Mehul Mehta, Chandra Sahajwalla, Mehul Desai, Patrick Marroum, Joga Gobburu, Yaning Wang, Peter Lee, Peter Hinderling, John Hunt, John Lazor, Bob Powell, Angela Minn, Roshini Ramchandani, Robert Kumi, Shew Mei

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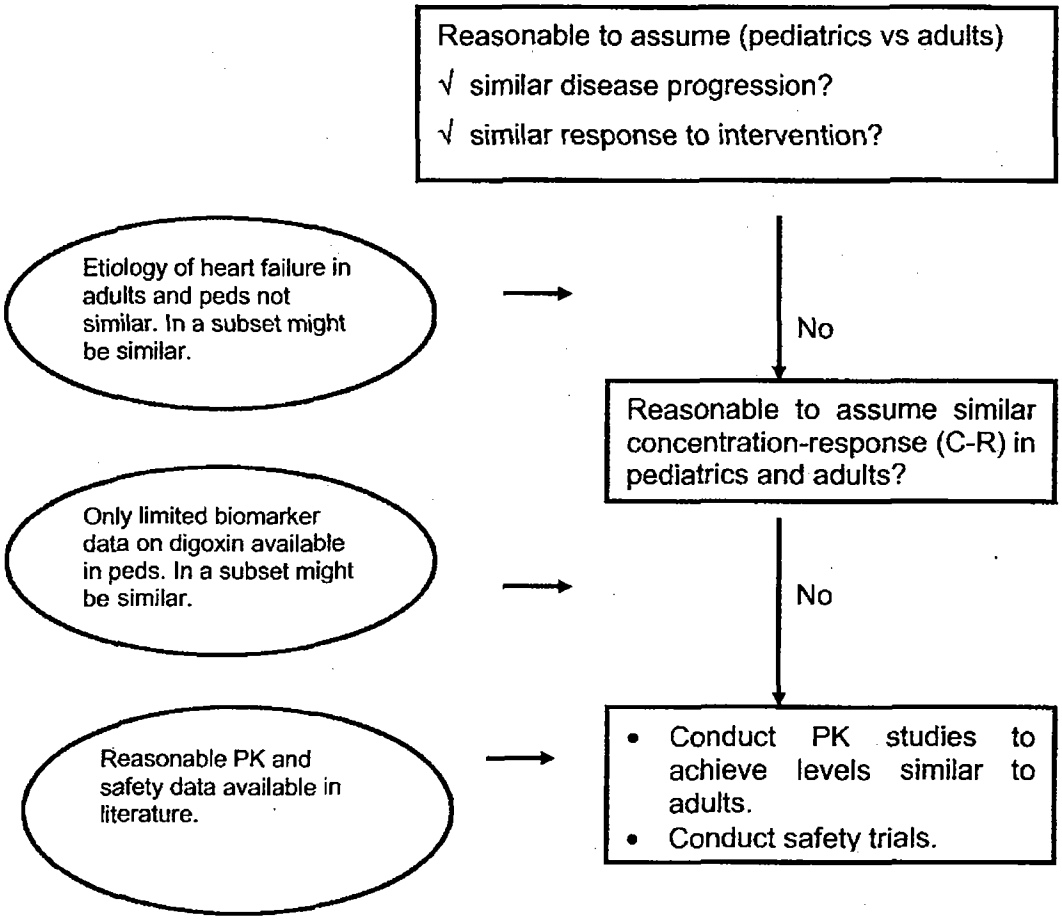
Summary of OCPB Findings

Roxane Laboratories has submitted a 505(b)(2) New Drug Application for Digoxin Elixir 0.05 mg/mL (NDA 21648). Digoxin (Lanoxin® tablets) is currently approved for heart failure and atrial fibrillation in adult and pediatrics (> 2 years). The review focused on three main topics. (1) Bioequivalence of elixir formulation (compared to Lanoxin® tablets) (2) Evidence of effectiveness of digoxin in pediatrics (primarily < 2 years) (3) Updating intrinsic/extrinsic factors in the label.

Based on the submitted information by the sponsor (as published literature) and also literature independently collected by the reviewer

1. Based on the Division of Scientific Investigations (DSI) prompted re-analysis, the pediatric formulation has been found to be bioequivalent to LANOXIN® tablets under fasted (90% CI: Cmax: 97.0-120.9; AUC0-t: 88.7-101.0; AUC0-∞: 89.6-105.1) and fed (90% CI: Cmax: 92.3-119.7; AUC0-t: 94.2-116.2; AUC0-∞: 94.2-122.1) conditions. This finding supports the applicability of the labelling of the digoxin tablets (which is approved for patients older than 2 years of age) to the elixir.
2. The pharmacokinetics of digoxin in pediatrics < 2 years of age are reasonably well characterized in the more recent studies. The pharmacokinetics from earlier studies should be interpreted with caution primarily due to the inaccurate assay method employed. Also, the lack of adequate description of the formulations used confounds interpretation of the results (for example, relative bioavailability of elixirs could be different by 50%).
3. The etiology of the diseases (atrial fibrillation and heart failure) in adults and pediatrics do not seem to be similar. It seems that atrial fibrilation is not a typical pediatric disease and cannot be compared to that in adults. Heart failure in pediatrics is congenital rather than due to coronary heart disease or hypertension as commonly observed in adults. However, pediatric cardiologists (

[redacted] opined that a subset of pediatrics have similar etiology as adults and might benefit from digoxin's ionotropic effect. This thinking is presented in the pediatric decision tree below for the heart failure indication.



4. For the heart failure indication, the concentration-contractility index relationship of digoxin in pediatrics is unknown. The little information available, at best, suggests that at the 'apparent' concentrations of about 1.7 and 3.5 ng/mL produce similar effects on contractility index in pediatrics (< 2 years). Unfortunately it is not known whether lower concentrations also

produce this effect, whether higher concentrations do not produce any further effect and what the true concentrations are if assayed well. It should be noted that concentrations in this range showed a plateau effect in adults for a different contractility index. No clear evidence on the optimum exposure of digoxin needed for treating heart failure in the pediatric population is available.

5. The medical reviewer should assess if the opinions put forth by the pediatric cardiologists [redacted] regarding the use of digoxin in a "subset" of pediatric population who might benefit from its ionotropic effect are convincing or not. Even if a relevant sub-population exists, there is inadequate information to recommend rational dosing for pediatrics under 2 years of age, as discussed below.
6. The dosing scheme proposed by the sponsor for pediatric patients is not justified and hence unacceptable. One of the reasons for not accepting the sponsor proposed dosing is the use of inaccurate PK information from a publication which used a poor analytical technique. Endogenous digoxin like substances, which are at high levels in neonates and infants, interfere with the measurement of exogenous digoxin. This concern can be alleviated by using PK data from the more recent publications. The more important reasons for not being able to recommend dosing for the less than 2 year patients are:
    a. Knowledge on how digoxin affects clinical outcomes is absent in pediatrics.
    b. Digoxin was shown to effect some relevant biomarkers and also shown to improve clinical outcomes in adults. A reasonable approach would be to characterize digoxin's effect on biomarkers in pediatrics to derive rational dosing guidelines. This approach has been used for other products. Although the concentration-biomarker relationship is

characterized for adults, it is not for pediatrics. It is not entirely clear if similar concentrations produce similar effects in both populations. Unfortunately, even the biomarkers used in adults and pediatrics were also different.

c. Patients < 2 years of age (neonates and infants) are the most heterogenous with respect to physiology and PKPD in them is poorly understood in general. This limits generalization based on data from older populations.

d. Inspite of having the mortality/morbidity data, the target concentration even in adults is not well characterized. The target concentration has been lowered in the more recent past (1.5 to 1 or 0.5 ng/mL). Now, it is needless to mention that targeting the concentrations in adults for deriving pediatric dosing has assumptions that are not fully justifiable.

e. The most critical factor that prohibits making assumptions when deriving dosing for pediatrics is the variability and narrow therapeutic index of digoxin that is well accepted in clinical practice. Inherently digoxin, given its target window, is a highly variable drug and additionaly it interacts considerably with several other potential concomitant medications. Hence managing safety is very likely a concern.

f. Of some concern is the lack of adequate information regarding the formulation used in the published literature. It is known that equal doses of two digoxin elixirs could lead to exposures that are different by about 50%. This makes interpretation of the PK data, which would be used to derive dosing recommendations, not so reliable.

Overall, given the several uncertainties in identifying the target population, a rational target concentration in pediatrics, narrow therapeutic window and high unexplained variability, deriving meaningful dosing guidelines for pediatrics < 2 years of age cannot be made without unverifiable assumptions.

7. In view of the narrow therapeutic index of digoxin and reported serious adverse events due to drug interactions, the current label has been updated to reflect the current understanding of various intrinsic/extrinsic factors to make the usage of digoxin safer, especially to make the medical community aware of the potential interactions (both pharmacokinetic and pharmacodynamic). The updated label has a total of about **145** interactions reported with digoxin in thePhysicians Desk Reference and the literature until 2004.

Question Based Review

A. General Attributes of Digoxin

1. What is the current submission about?

Roxane Laboratories, Inc. has submitted a 505(b)(2) New Drug Application for Digoxin Elixir 0.05 mg/mL. The objective of this New Drug Application (NDA 21-648) is to seek approval for the use of Digoxin Elixir, 0.05 mg/ml for the treatment of mild to moderate heart failure and atrial fibrillation in adults and pediatrics older than 2 years of age.

2. What is the regulatory history of digoxin?

Digoxin has been in clinical use well before the passage of the Keafauver-Harris Amendments of 1962. Oral digoxin (NDA# 018118) first received official Agency approval in 1982 primarily on the basis of literature references. The approved formulation was that of a digoxin solution in a capsule (Lanoxicaps). In the early 1990's, an NDA (NDA#20-405) was submitted for digoxin tablets (Lanoxin). Because this tablet formulation was not bioequivalent to Lanoxicaps, it could not be approved via an abbreviated NDA. The tablet formulation (NDA#20-405) received data dependant approval in 1994 on the basis of the RADIANCE (**R**andomized **A**ssessment of **D**igoxin on **I**nhibitors of **AN**giotensin-**C**onverting-**E**nzyme) and PROVED (**P**rospective **R**andomized **S**tudy of **V**entricular **F**ailure and **E**fficacy of **D**igoxin) studies that were randomized, parallel group, placebo-controlled withdrawal trials. In 1997, after the completion of the DIG (**D**igitalis **I**nvestigation **G**roup) study, the labeling to Lanoxin was updated to reflect the current understanding of digoxin.

Roxane Laboratories, Inc. has marketed the elixir formulation since 1988 under the brand name Digoxin Elixir USP, 0.05 mg/mL. In the November 24, 2000 *Federal Register,* the Food and Drug Administration (FDA) notified drug

companies that it required submission of drug applications and bioavailability tests for all oral digoxin products. Roxane submitted a response on February 16, 2001, stating that the product was medically necessary and should remain on the market until such time that a New Drug Application (NDA) could be submitted to the FDA. Roxane requested that FDA extend the effective date for requiring approved marketing applications after publication of the final rule from 30 days to two years. A meeting was held between Roxane and the FDA Divison of Cardio-Renal Drug Products on March 27, 2002 to discuss the submission of a 505(b)(2). During this meeting, the FDA agreed to defer regulatory action because a new drug application was being actively pursued, and the product is of a medically necessary nature.

Therefore, as agreed upon by the FDA in the March 27, 2002 meeting, this 505 (b)(2) application is being submitted for Digoxin Elixir USP, 0.05 mg/mL. Preclinical and clinical information, as previously mentioned, will be extensively cross-referenced. Labeling has been updated to reflect a recent review of the literature. It is Roxane's position that there are no safety or effectiveness concerns with Digoxin Elixir USP, 0.05 mg/mL.

Also at that meeting, it was agreed that the application should satisfy two main requirements:

1. Bioequivalence Studies: Roxane Laboratories would demonstrate bioequivalence for their elixir to RLD (Lanoxin®) tablets. Studies were to be conducted in both fed and fasted patients. A demonstration of bioequivalence to the RLD would be sufficient to meet the Agency's standards for bioequivalence.
2. Pediatric Data: Roxane Laboratories, Inc would supply data to justify any proposed pediatric labeling . Effectiveness and safety information included in the label and the basis for the instructions for use would need to be justified by referencing the available literature, or, a very strong case made for why this is not possible/relevant.

4. What is the proposed mechanism of action of digoxin?

The mechanism of hemodynamic effects of digitalis glycosides has been described adequately in the literature[1, 2]. The Na, K-adenosine triphosphate (Na, K-ATPase or Na, K-pump) mediates the active transport of Na out and K into the cell and has been identified in virtually all animal tissues including human myocardium. The active Na and K transport is specifically inhibited by cardiac glycosides. While there is no doubt that cardiac glycosides are effective in heart failure, the underlying mechanisms are still debated.

Two major mechanisms are of major importance for their hemodynamic effects, that is their positive ionotropic (See Figure 1) and their neurohumoral effect.

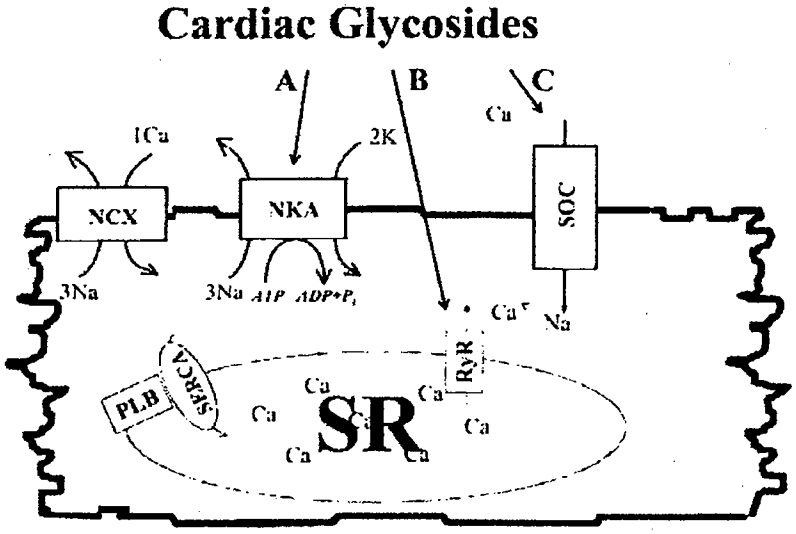


Figure 1. Mode of ionotropic action of cardiac glycosides.

Three different pathways have been proposed to mediate the positive inotropic effect of cardiac glycosides. (A) Cardiac glycosides bind with high affinity to the Na, K- ATPase (NKA) and inhibit enzyme activity. Thereby, intracellular Na is increased and the driving force for the Na, Ca- exchanger (NCX) to extrude Ca from the cell is reduced. The remaining Ca is accumulated in the sarcoplasmic reticulum (SR) via the SR Ca- ATPase (SERCA) and is released during subsequent depolarizations leading to enhanced contractility. (B) The Ca-

release from the SR has been found to be enhanced secondary to the interaction of cardiac glycosides with the Ca- release channel (ryanodine receptor, RyR). (C) Cardiac glycosides lead to a 'slip- mode' conduction of sodium channels (SOC) allowing Ca- ions to enter the cell via the channels. The interaction of cardiac glycosides with SOCs may be either direct or indirect (via NKA).

Besides their direct positive ionotropic effect, cardiac glycosides improve hemodynamics also by inhibition of extra-cardiac Na, K-ATPase.

B. General Clinical Pharmacology

1. What is the evidence of effectiveness of digoxin in adults and pediatrics?

This question will be addressed for both heart failure and atrial fibrillation. The findings in adults are first discussed followed by findings for pediatrics. The pertinent literature was reviewed and is summarized below:

Evidence of Effectiveness in Atrial Fibrillation

Adults

The relationship between plasma concentrations of digoxin and heart rate were examined in adults in an acute atrial fibrillation trial[3]. The Digitalis in Acute Atrial Fibrillation (DAAF) trial was performed in order to study the effects of intravenously administered digoxin on heart rate and the probability of conversion to sinus rhythm in patients with acute atrial fibrillation.

Study Design	Randomized, double blind comparison of intravenously administered digoxin and placebo in patients with atrial fibrillation.
Primary Endpoint	Conversion to sinus rhythm within 16h after randomization.
Secondary Endpoint	Effects on heart rate and safety.

PK/PD relationship

Due to the high frequency of spontaneous conversion to sinus rhythm in the placebo group and the lack of statistical difference in the conversion rate between placebo and the active treatment, PK/PD modeling was not performed for the primary endpoint. Hence, a PK/PD model was developed for the secondary endpoint, heart rate.

A two compartment model best described the time course of digoxin concentrations in plasma. Digoxin and creatinine clearance correlated strongly and mean plasma concentration of digoxin at 16h was within recommended levels (1.6±1.0 nM or 1.28±0.80 ng/ml). A link model assuming a slow equilibration to the effect compartment was used due to the well known delay in response after intravenous administration of digoxin. The degree of reduction was related to the initial heart rate and patients with higher heart rate had more pronounced decrease. The decrease in heart rate was linearly related to the estimated digoxin concentration at the effect site (Figure 2).The decrease in heart rate in placebo-treated patients was, on average, 0.5 bpm per hour. The model predicted that a digoxin concentration of 1nM (0.8 ng/ml) at the effect site reduces heart rate by 9.4%.

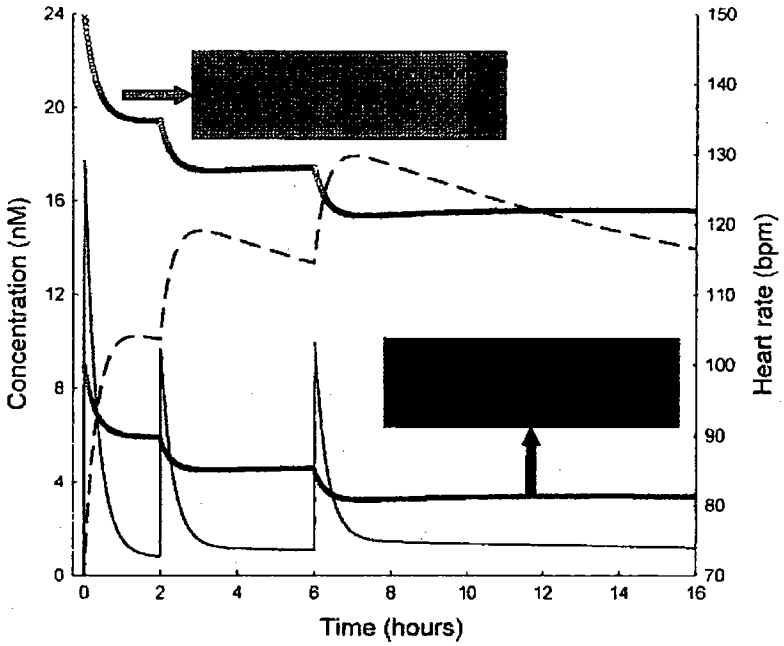


Figure 2. Typical concentration-time profiles for digoxin in plasma (solid line) and effect compartment (broken line, scaled upwards with a factor of 10 only for the purpose of graphing) with bolus doses 0.5, 0.25 and 0.25 mg given i.v. at 0, 2 and 6 h.

Treatment with digoxin did not increase the rate of conversion to sinus rhythm (Figure 3)

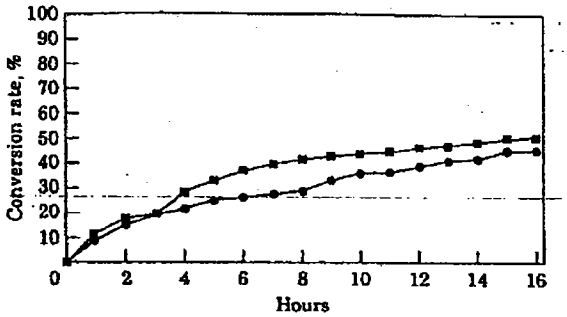


Figure 3. Conversion to sinus rhythm over time. Results are expressed as percent of sinus rhythm in total group (●=Placebo; ■=digoxin).

Pediatrics

There are no data available to evaluate the effectiveness of digoxin for atrial fibrillation in pediatrics.

It should be recognized that atrial fibrillation is found in 1% of persons older than 60 years to more than 5% in patients over 69 years old. Sinus tachycardia is common in infancy and early childhood and is the normal reaction to a variety of physiological or pathological stresses such as congestive heart failure etc. Atrial flutter occasionally can be congenital or can follow surgery for congestive heart failure or can even occur in utero. Atrial flutter tends to be unstable, reverting to sinus rhythm or degenerating into atrial fibrillation.

Evidence of Effectiveness in Heart Failure

Briefly the findings from large clinical trials and also studies which were based on non-invasive measures of cardiac function will be discussed here.

Adults

The evidence of effectiveness and safety of digoxin in adults was obtained from several clinical trials. Notably among them was the large multicenter **D**igitialis **I**nvestigator **G**roup (DIG) Trial, composed of 2 studies in a total of 302 centers in the United States and Canada in 6800 patients[4]. After a mean follow up of 37 months (range, 28-58 months), there was no effect on mortality from digoxin therapy at serum concentrations of 0.5-2 ng/mL, but the study did find that hospitalization due to worsening heart failure was modestly reduced.

In addition to DIG trial, there were two prospective, multicenter, placebo controlled trials that examined the effects of withdrawl of digoxin in patients with stable mild-to-moderate heart failure (ie., New York Heart Association [NYHA] class II or III) and systolic ventricular dysfunction (ie., a left ventricular ejection fraction ≤ 0.35). The two trials were PROVED (**P**rospective **R**andomized Study **O**f **V**entricular failure and **E**fficacy of **D**igoxin) and RADIANCE (**R**andomized **A**ssessment of **D**igoxin on **I**nhibitors of **AN**giotensin **C**onverting Enzyme)[5, 6]. All patients studied were in sinus rhythm; the target serum digoxin concentration in both studies during the baseline run-in phase was 0.9-2.0 ng/ml; and in RADIANCE, patients in the trial also received concurrent therapy with an ACE inhibitor. When patients were randomly assigned either to continue active

digoxin therapy or to withdraw from active therapy and receive matching placebo, 40% of patients in PROVED and 28% of patients in RADIANCE who received placebo noted significant worsening of heart failure symptoms compared with 20% and 6%, respectively, of patients who continued to receive active drug.

Non-invasive Measures of Digoxin Effect

In several other studies, various investigators used non-invasive measures to quantify the ionotropic effect of digoxin. Similar measures have been used in pediatrics also. Systolic time intervals (STI) were used for this purpose[7]. Investigators have focussed on the measurement of three STI: total electromechanical systole (QS_2), left ventricular ejection time (LVET) and the preejection period (PEP).

In a single dose (1 mg intravenous) study in 12 healthy male volunteers serum digoxin concentrations and systolic time intervals were obtained from simultaneous tracings of electrocardiogram, phonocardiogram and carotid arterial pulsations[8]. The electromechanical systole corrected for heart rate (QS2I) was calculated and changes in QS2I (ΔQS2I) were determined as the difference between control and experimental values.

Figure 4 below shows the time course of digoxin serum concentrations and response

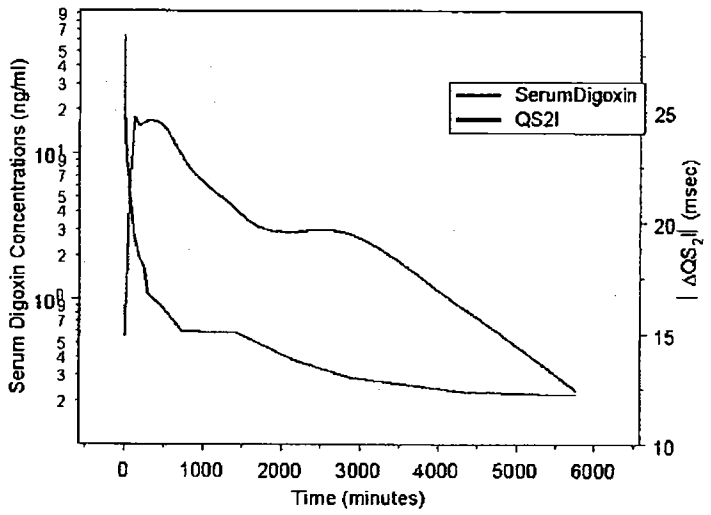


Figure 4. ...ıe data after a rapid i.v i

The investigators observed that the maximum response was observed at 180 minutes post intravenous dose. A three compartment model was used to explain the time course of serum concentrations of digoxin. The investigators report that a nonlinear function could best describe the relationship between predicted tissue concentrations of digoxin and response.

In another report, the model developed in this study was used to predict the relationship between steady state post-distributive (>8h) serum concentrations of digoxin and QS2I (response)[9]. Figure 5 below shows the predicted non-linear relationship between response (percent of maximum) at 24h after digoxin dose and the concentrations of digoxin at the same time.

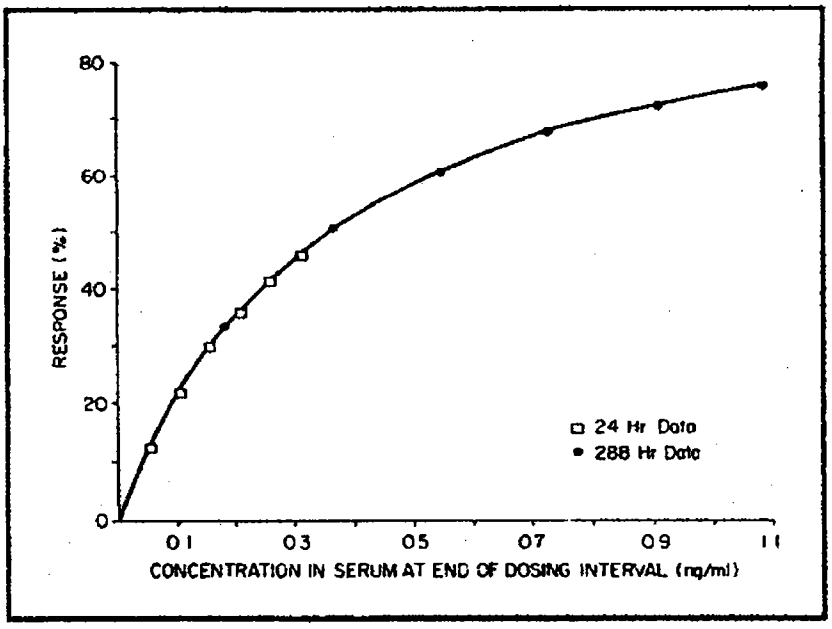


Figure 5. Nonlinear relationship between response (percent of maximum) at 24 hours after a digoxin dose and the concentration of digoxin in adults.Based on the simulations (□- single oral doses of 0.125-0.75 mg; •- multiple oral doses of 0.125-0.75 mg every 24 hours for 12 days), the investigators state that the

"therapeutic levels" of digoxin refer to the "flat" portion of the serum concentration-response relationship.

In another study, serum digoxin concentration and time intervals were measured in 21 adult patients [10] receiving 0.25 mg digoxin daily. The daily dose was increased to 0.5 mg and measurements were repeated 5 to 7 days later. Serum digoxin concentrations were 0.56±0.06 ng/ml and increased to 1.18±0.11 ng/ml with the larger dose. Associated with the increased serum digoxin was a mean increase in duration of total electromechanical events of 6.3±2.9 msec ($p<0.025$) and a mean shortening of left ventricular ejection time of 5.6±3.0 msec ($p<0.05$). The mean decrease in preejection phase of 1.1±2.1 msec.

In nine adult patients the digoxin dose was randomly varied between 0 and 0.75 mg/day and measurements were made 4 to 5 days after drug administration at each dose level. The correlation coefficient between changes in serum digoxin and changes in left ventricular ejection time was –0.55 msec ($p<0.01$) (Figure 6 and 7).

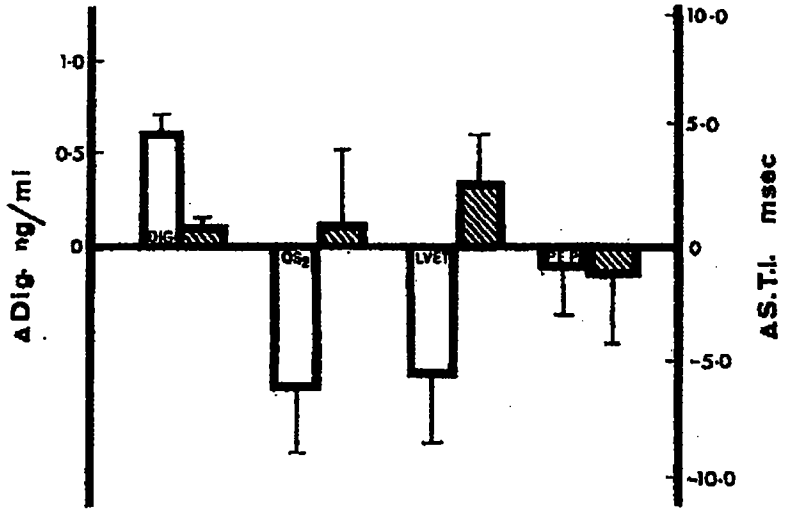


Figure 6. Relationship between digoxin concentrations and changes in STI.

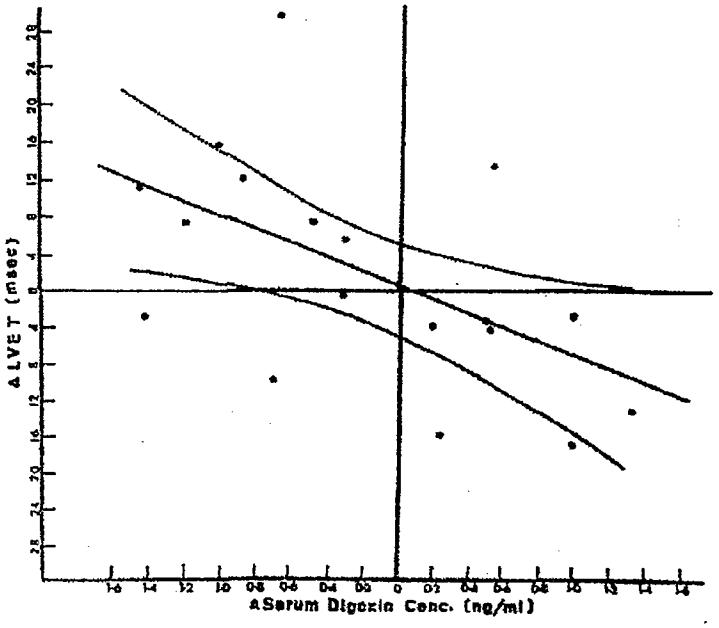


Figure 7. Relationship between changes in LVET and serum digoxin concentrations.

Pediatrics

There is no clinical trial that has prospectively evaluated the effectiveness of digoxin in pediatrics for heart failure using the rigorous standards that are used by the Agency for approval of treatments. However, one should realize that a trial with outcomes or surrogates such as exercise capacity as observed in adults is not possible in pediatric population (specifically neonates, infants). It is important to note that heart failure in pediatrics is congenital rather than due to coronary heart disease or hypertension as commonly observed in adults. The defects most likely to cause heart failure from structural defects include left-to-right shunt lesions (eg., ventricular septal defect, common atrioventricular canal defect, patent ductus arteriosus, aorticopulmonary window, truncus ateriosus), left heart obstructive lesions (eg., critical aortic stenosis, severe aortic coarctation, congenital mitral stenosis) and congenital atrioventricular or semilunar valve regurgitation. The positive ionotropic effect of digoxin is clinically

indicated by improvement of the patients general condition, and decrease in liver and heart sizes as well as respiratory and cardiac rate. Some of these parameters are hard to measure in an objective manner in newborns and infants, others are greatly dependent on extracardiac effects. To judge the clinical effect of digoxin in this age group it is, therefore, desirable to measure an indicator of myocardial contractility using a method which is noninvasive, innocuous and repeatable at will. Echocardiography fulfills these latter criteria.

The data that have been published in literature in the 70's and the 80's in small, uncontrolled trials is discussed here. The studies have used noninvasive measures such as systolic time intervals etc to measure the effect of digoxin from baseline whose relation to outcomes is not known.

Alterations in the sensitivity of the human heart to digoxin[11]

Digoxin doses of 10 μg/kg/day and 40 μg/kg/day were administered to 8 and 10 neonates under four weeks of age. The drug was given in divided doses every 12h and venous blood samples were collected for radioimmunoassay of digoxin 6-8h following an oral dose after at least five days constant therapy. Digitalization was undertaken for heart failure due to wide spectrum of cardiac diseases. Electrocardiographic monitoring was performed. There was a similar clinical response in both high and low dose groups of neonates. Clinically, no additional benefit or adverse effect in the form of toxicity was determined in the high dose group. In the low dose group, the plasma 'apparent' digoxin concentration was 1.5±0.3 ng/ml (1.1-1.8 ng/ml) and in the high dose group 2.5±0.4 ng/ml (1.9-2.9 ng/ml). Thus for a four fold increase in dose a 1.7 time increase in plasma concentration of drug was found. There was no evidence of electrocardiographic toxicity in either group. Maximal ionotropic effect, as measured by systolic time intervals, usually occurs with small doses of digoxin.

Effects of digoxin on systolic time intervals of neonates and infants[12]

Systolic time intervals were measured in 27 normal new born infants before and after administration of oral digoxin (30 µg/kg). Systolic intervals were also measured in 10 newborns and infants with congestive heart failure before and after this same 30 µg/kg dose of digoxin, but also after administration of a much larger "digitalizing dose" of 80 µg/kg. Preejection period (PEP) shortened significantly, relative to baseline, in the normal new borns and those with congestive heart failure following the smaller dose. Changes in ejection time (ET) were much less striking and appeared to be transient, less than 8h. In general, larger doses produced no further changes in PEP or ET, although there were exceptions. The study showed that the maximal ionotropic effect, as measured by PEP changes, usually occurred with small doses of digoxin.

Dosage of digoxin in premature infants[13]

The work by Pinsky et al as described below has often been cited as proof of effectiveness in premature infants.

Aim: To establish guidelines for the use of digoxin in premature infants. Pinsky et al conducted the study in 37 infants. The infants were divided into two groups.

Phase I: In Phase I of the study, 25 infants received a total dose of 30 ug/kg dose intravenously. One half of the dose was administered immediately, then one-fourth was given 8-12 hours after the first dose and the remaining one-fourth was given another 8-12 hours later. The maintenance dose was one eighth of the total dose given every 12 hours.

Phase II: In Phase II of the study, 12 infants received a total dose of 20 ug/kg dose intravenously. One half of the dose was administered immediately, then one-fourth was given 8-12 hours after the first dose and the remaining one-fourth

was given another 8-12 hours later. The maintenance dose was one eighth of the total dose given every 12 hours.

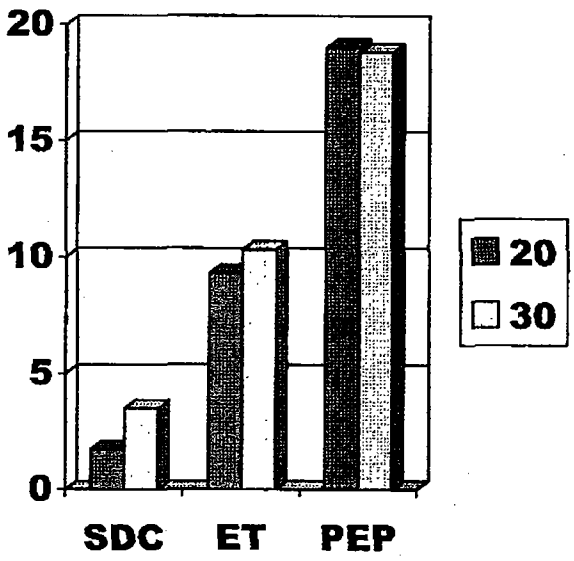
Pharmacokinetics: After receiving a minimum of four maintenance doses blood was drawn to measure digoxin serum concentration. The sample was drawn 12 hours after a maintenance dose.

Analytical Method: Blood samples were analyzed by RIA technique (Quantitope).

Results

Pharmacokinetics: The range of serum digoxin concentrations in Phase I were 1.4-7.5 ng/mL (Mean 3.5±0.39 ng/mL). In Phase II the concentrations were 1.2-3.0 ng/mL (Mean 1.73±0.15 ng/mL).

Cardiac Effects: Seven patients in Phase I and six patients in Phase II had pre- and post digitalization electrocardiograms. The graph below shows the cardiac effects measured during maintenance therapy after digitalization with 20 and 30 ug/kg dose.



Conclusions

The investigators conclude that 20 ug/kg be used as the total dose for digitalization in premature infants.

Reviewer Questions

The following questions however remain answered to accept the study as proof of effectiveness in premature infants:

1. The analytical method used by the authors has been reported by Hastreiter not able to distinguish between digoxin and EDLS. This would raise questions on the reported concentrations of digoxin.
2. The maintenance dose used in the study is 5-7.5 ug/kg/day. Cardiac effects were measured during the maintenance therapy. However, this does not constitute as proof of evidence that adequate effectiveness is achieved at low doses. How confident are we that the effects are not in the lower portion of the dose-response curve?
3. The authors did not measure the cardiac effects in all the patients in the study. In only few patients the effects were measured. The authors do not indicate the serum digoxin concentrations in these patients.

Non-invasive assessment of left ventricular function related to serum digoxin levels in neonates[14]

To establish if patients with higher serum digoxin concentrations showed any difference in systolic time intervals in comparison to patients with lower levels of digoxin. Eighteen neonates, all under 1 month of age and in cardiac failure formed the study group. Nine patients had levels of 1.99±0.35 ng/ml while nine others had 3.62±0.95 ng/ml. Therapy with digoxin produced changes in heart rate and systolic intervals in both groups. Both showed significant shortening of electromechanical systole index. Statistical analysis showed that the two groups were not significantly different.

Effects of digoxin on left ventricular contractility in newborns and infants estimated by echocardiography[15]

Patients: New borns and infants with congestive heart failure

Assessment: 2-4 h after first digoxin dose as well as after full digitalization.

Dose: The digitalizing dose with digoxin in new borns was 0.034 mg/kg body weight orally or 0.028 mg/kg body weight intravenously, respectively. Infants received 0.07-0.08 mg/kg body weight orally. Half of the digitalizing dose was given as first dose, followed by ¼ after each 8 and 16h, respectively. The daily maintenance dose was ¼ of the digitalizing dose, divided into two equal doses.

Methods: The echocardiograms were recorded in a standard manner for small children to measure left ventricular enddiastolic diameter (LVED), left ventricular endsystolic diameter (LVES), left ventricular preejection period (LVPEP), left ventricular ejection period (LVET). The mean values of the measurements of five cardiac cycles were used for the calculation of shortening fraction of the left ventricular minor diameter (SF) and mean circumferential shortening (mV_{cf}).

Results: The plasma concentrations of digoxin ranged between 1.6-4.4 ng/ml. The study clearly shows an increase of SF and mean Vcf in newborns treated with a low dose of digoxin (Figure 8).

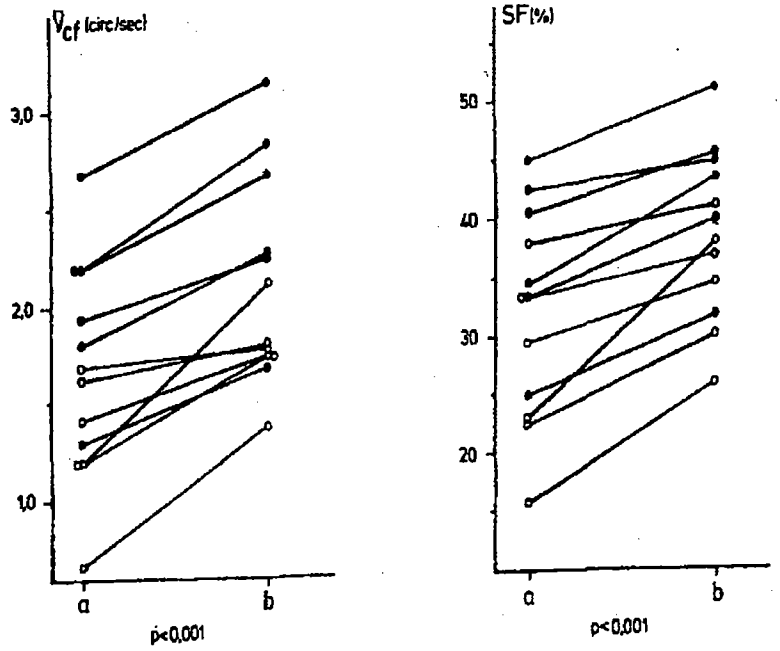


Figure 8. Change in mean Vcf and SF before (a) and after (b) digitalization with digoxin. (•=new borns; ○=infants)

No indication of intoxication was observed.

Overall conclusions for heart failure in pediatrics

Biomarkers/Surrogate Markers

In chronic heart failure, the impact of the drug therapy on mortality is a crucial issue that can best be answered by large expensive mortality trials. However, biomarkers/surrogate markers can help to circumvent the need for these trials, only if there is sufficient evidence to show that drug therapy which alters mortality also causes a corresponding change in the surrogate. The effect of drug therapy

on various surrogate markers in chronic heart failure in adults are shown in the table below.

Drug	Mortality	Heart rate variability	Heart rate	baroreceptor sensitivity	QT dispersion	Holter arrhythmias/ signal-averaged ECGs	Neuro-hormones
ACE inhibitors	G	G	G	G	G	G	G
β-blockers	?G	G	G	↓↑	G-n	G	G
Digoxin	O	G	O/G	G	?	O	G
Diuretics	?	?	O/G	?	?	↓↑	B
Ibopamine	B	G	O	?	?	O	G
Ca-antagonists	O	O-n	O/B	G	?	?	O
Hydralazine-nitrate	G	?	B	?	?	O	B
Flosequinan	B	?G	B	?	?	?	B
Milrinone	B	?	?	?	?	B	B
Class I: Flecainide	B	B	O	?	?	↓↑	?
Class III: Amiodarone	O/G	G	G	?	G	G	?

G=good effect; B=bad effect; O=neutral effect; ?=not known; ↓↑=conflicting data; n=effect documented in non-CHF patient.

It was previously considered that ejection fraction is a potential surrogate endpoint for survival in patients with heart failure. However, its positive predictive value is low and inotropic drug therapy such as milrinone, which improved ventricular function, had opposite, adverse effect on mortality[16]. Hence, surrogates other than ejection fraction will need to be considered. Neurohormonal antagonists such as ACE inhibitors and beta-blockers, seem to benefit both mortality and all surrogate markers of mortality. However, significant discrepancies exist, particularly for digoxin, ibopamine and hydralazine-nitrates, although it is in the latter two that diametrically opposite events occurred, whereby favourable surrogate effects turned into unfavourable mortality effects (or vice versa)[17]. Perhaps a battery of surrogates would be more appropriate rather than being any single surrogate. Unfortunately these are not known at the present time.

Concentration-biomarker relationships

The studies reviewed here show that digoxin alters the indices reflective of its positive ionotropic effect. It appears that changes in the contractility indices in pediatrics are in the "flat" portion of the concentration-response curve as shown for adults in Figure 5. The published articles do not substantiate well the choice

of the target population. It is vague whether the pediatric patients studied should be receiving digoxin in the first place. Taking all the above studies into account, the dose range tested is from 5 to 80 ug/kg/day (1.7 ng/mL to 2.5 ng/mL for 40 ug/kg/day; concentrations at 80 ug/kg/day were not measured). The relationship between the contractility indices and clinical outcomes is unclear. Also, it is not obvious if dose lower than 10ug/kg/day produce lower effects. Typically the Agency has accepted concentration-biomarker relationships from studies without placebo data, especially in pediatrics. However, the Agency did have effects over a reasonable range to identify meaningful target concentrations. Further, such data used the same biomarker in adults and pediatrics. Where similar biomarkers were measured in the two populations the results presented did not allow direct comparison. For example, authors of reference#10 measured LVET in adults and presented as change in digoxin concentrations from previous dose versus change in LVET from baseline. Authors of reference#13 measured LVET in pediatrics but presented the digoxin concentrations and percent change in LVET.

In conclusion, first the biomarker and clinical outcome relationship is questionable and second, even if it is not quantitative comparisons, between pediatrics and adults, are not possible with the available data.

3. What is the toxicity profile of digoxin in pediatrics, especially < 2 years of age?

Therapeutic serum digoxin concentrations in most adult patients without clinical evidence of toxicity vary between 0.5 and 2.0 ng/ml, while those exhibiting toxicity are in excess of 2.0 ng/ml[18, 19]. It is important to note that there are numerous reports in the literature about the potential issues with the analytical methods used previously to measure digoxin.

In pediatric patients, digoxin toxicity is difficult to detect. Poor feeding and weight loss are possible signs of toxicity. However, weight loss in infants with severe

congenital heart disease can be caused by the effects of the disease. Vomiting, atrioventricular block and supraventricular arrhythmias have been reported to be more frequent manifestations of digoxin toxicity in pediatric patients than in adults. The final diagnosis of digoxin toxicity requires both clinical and electrocardiographic data as well as serum concentrations of digoxin.

The summary of the serum concentrations and toxicity symptoms are shown in table below.

Patient Age	Prevalence	Serum digoxin Concentration, ng/ml	Toxicity
1-20 days	14/46	1.5-16.7 (mean 7.6)	Bradycardia, AV block, increased PR interval
<30 days	3/10	4.1-5.9 (mean 4.4)	PVCs, tachycardia, AV block, AF, AT
<30 days	9/18	4.5-5.3	Bradycardia, arrhythmias, feeding problems
2 days-5 months	12/34	2.7-12.8 (mean 4.7)	Vomiting, AV block, PACs, bradycardia, AFL
1 week-11 months	5/31	3.8-8.6 (mean 5.6)	Atrial and AV conduction disturbances
0.5-12 months	6/35	3.6-10.5 (mean 7.0)	Vomiting, bradycardia, heart block, tachycardia
5 months-16 years	1/15	≤3.3	Primary AV block
	4/11	>3.3-6.5	Bradycardia, ST depression
	3/5	> 6.5-9.9	Increased PR interval, bradycardia
	4/6	>9.9-13.1	Primary and secondary AV block, bradycardia
	4/4	>13.1-14.9	Increased PR interval, primary and secondary block
Children (mean 3 years)	11/35	2.2-8.7 (Mean 6.3)	ECG changes, aberrant rhythm
5 to 12 years	4/57	2.2-5.1 (mean 8.4)	ECG changes, SVT, AV block
Adults	4/24	Mean 3.7	VA
32-80 years	23/48	3.2-7.6	ECG changes, rhythm and conduction disturbances

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5. What are the pharmacokinetic characteristics of digoxin in adults and pediatrics?

The pharmacokinetics of digoxin has been well studied in all age groups from 0.1-70 years[20-32].

The following terms are used to define various age groups.

Category	*Age*
Premature	Born at < 37 weeks gestation
Term	37-42 weeks gestation
Post-term	>42 weeks gestation
Neonate	0-1 months
Infants	1-12 months
Child	1-12 years
Adolescent	12-18 years
Adult	>18 years

The salient features of absorption, distribution, metabolism and elimination of digoxin in various populations is discussed below.

Oral Bioavailability

Digoxin is absorbed by a passive, nonsaturable process in the upper part of the intestine. Its absorption is rapid in fasting state but extent of absorption is not affected by coadministration with food. Peak serum concentrations are reached within 30-90 and 360 minutes after therapeutic and acute doses respectively. The oral bioavailability was 72% in neonates, adults etc (Range: 52-79%).

Distribution

The disposition characterized by a two compartment model and the distribution phase ranges from 20-60 minutes. Digoxin has a large volume of distribution due to extensive tissue binding. Similar relative distribution of the glycoside in infants and adults: choroid plexus>ventricular myocardium>kidney>liver>skeletal muscle was observed. The ratio between myocardial (ventricular tissue) and

serum concentrations were found to vary from 47:1 to 174:1 in adults and from 70:1 to 175:1 in infants. In neonates and infants, myocardial digoxin concentration is highly variable but averages 2 to 5 times that of adults. The neonatal erythrocytes have two and half times digoxin-binding sites as adult erythrocytes. The mean binding of digoxin to plasma proteins ranged from 30.4-34% and was not different between various age groups.

Metabolism

Only a small fraction of digoxin is metabolized. The major metabolites are inactive digoxin reduction products (DRPs). No known age differences exist in the metabolic breakdown of digoxin.

The cardioactivity of digoxin metabolites is shown below.

Metabolite	% activity relative to digoxin
Dihydrodigoxin	2-6
Dihydrodigoxigenin	2
Digoxigenin	4-21
Digoxigenin mono-digitoxiside	66
Digoxigenin bis-digitoxiside	77

Elimination

Renal:

Renal clearance of digoxin occurs by glomerular filtration, tubular reabsorption and tubular secretion. In normal patients about 60-80% of the dose is excreted unchanged.

Non-renal:

Using segmental intestinal perfusion in humans, direct evidence was provided that intestinal P-glycoprotein mediates substantial drug elimination after intravenous administration from the systemic circulation into the gut lumen and prevents entry of luminally administered P-glycoprotein substrates into the enterocytes. Excretion of digoxin in bile has also been reported[32].

Age-related changes:

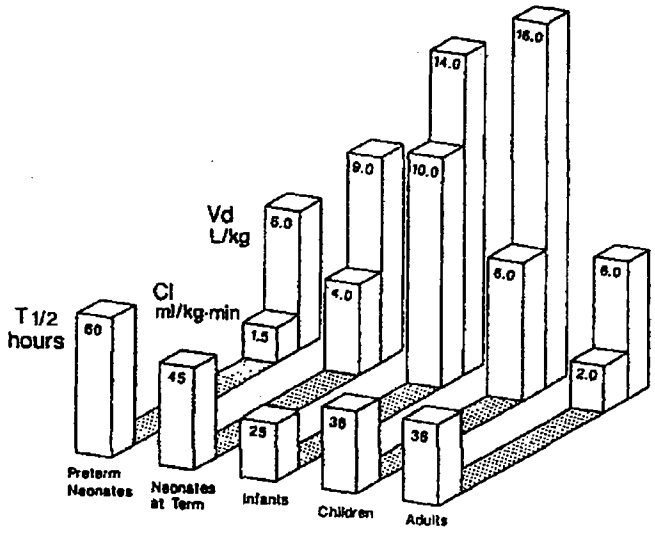
Total body and renal clearance of digoxin is low in early postnatal period and increases dramatically during the first weeks of life. The increase in digoxin renal clearance parallels the increase in creatinine clearance and reflects maturation of glomerular filtration and tubular secretion[31, 33-35].

Summary of Pharmacokinetic Parameters

The summary of pharmacokinetic parameters of digoxin in various age groups is shown in the table below[21-23, 29, 36-43].

Classification	Vd (L/kg)	CL (ml/min/kg)	T1/2β
Premature	3.5-6.0	0.75-1.4	35-170
Term	5.0-10.0	1.7-2.9	35-70
Infants	8.0-16.3	2.7-10.0	18-36
Children	8.6-12.8	2.8-6.0	36
Adults	5.0-7.5	1.5-4.0	36-50

Figure 9 below shows the relationship between digoxin clearance and volume of distribution versus age.



This has led to comments in various publications that infants clear the drug much faster than children and adults and hence may require larger doses. This is not a correct way to look at the influence of developmental pharmacology on the pharmacokinetics of digoxin. When bodyweight is standardized and disentangled from age, developmental changes can be understood more clearly. The relationship between digoxin clearance (L/day and L/day/kg) and age is shown in Figure 10 below based on data from literature[44]. When we use L/day/kg it shows that infants clear digoxin faster than adults, which is not seen when we use L/day. So to correctly view the relationship of clearance, weight and age, one should standardize bodyweight and disentangle it from age by using an allometry model such as $CL = CL_{std} \bullet \left(\text{Weight}/70\text{ kg}\right)^{0.75}$ [45].

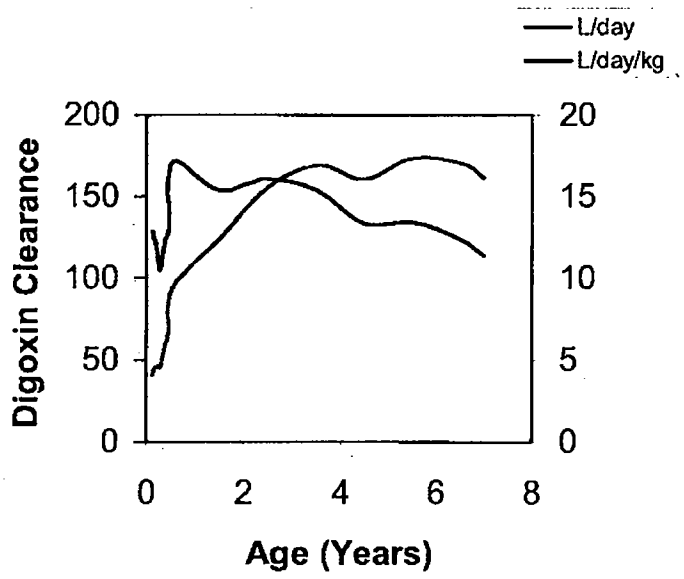


Figure 10. Relationship of digoxin clearance and age.

5. What are the proposed dosage(s) of digoxin in various age groups?

The sponsor proposes the following daily dosage requirements of digoxin in various patient populations:

The recommended initial estimates for daily oral doses of digoxin are

Age	Daily Oral Dose, µg/kg/day
[redacted]	
Prepubertal children	10
Adults	3

These doses will, in uncomplicated patients, tend to produce steady-state post-absorptive levels of 1–2 ng/mL, but the confidence limits around this range are wide. Hence therapeutic drug monitoring is required.

In a meeting with the sponsor on January 26th, 2004, the dosing recommendations proposed were discussed. The reviewer in the meeting indicated that the dosing recommendations as proposed by the sponsor are questionable. The sponsor indicated that they would look into the dosing recommendations and re-submit new dosing recommendations. Based on the discussions, the sponsor submitted new dosing recommendations which are as follows:

Age	Daily Oral Dose, µg/kg/day
[redacted]	
Prepubertal children	10
Adults	3

6. Is the dosing regimen proposed by the sponsor acceptable?

In a teleconference on February 10th 2004, the dosing recommendations proposed by the sponsor were discussed. The sponsor relied on the data published by Patterson et al and Hastreiter et al[46, 47].

The dosing recommendations by the sponsor are not acceptable for the following reasons:

1. The linear relationship between serum concentrations and dosage in various age groups as proposed by Hastreiter is biased. This is because of the intercept on the Y-axis being greater than 1 ng/mL. The high positive intercept is due to the (A) Assumption of linear relationship (B) Three different RIA kits used in the analysis of serum digoxin concentrations. These findings would make the regression equation showing the relationship between digoxin concentrations and dose unreliable to use for dosage recommendations.

2. Hastreiter et al in Table I (in publication) provide the estimates of clearance after oral administration. The reviewer used these values to calculate dosing recommendations.

3. Suematsu et al used powder formulation in their study. They report that the bioavailability from powder formulation is 25.3% less than that of elixir. In the dosage calculations, proposed by the reviewer, this difference was taken in account.

4. Dosing recommendations for age groups less than 1 year calculated based on Suematsu et al and Suarez et al are in good agreement for some age groups. These are however, quite different from Hastreiter etal.

5. The dosage recommendations for pediatric population to target 1.5 ng/mL based on published information by Suematsu, Hafstreiter, Patterson and Suarez are shown in table below.

Comparison of dosing recommendations by Suematsu, Suarez, Hafstreiter and Patterson. The labeling recommendations for age groups in LANOXIN tablets label is also shown here.

Age	*Suematsu*	*Suarez*	*Hastreiter Equation based*	*Hastreiter CL based*	*Patterson*	*LANOXIN tablets*
< 3months	15-16	12-14	1-2	2-5	3	-
3-6months	16-18	14-17	6	6	-	-
7-12months	18	18-22	8	8	-	-
1year	16	23	11	9	-	-
2-5year	12-14	-	10	8	-	10-15
6-10year	12	-	11	6	-	7-10
11-20 years	-	-	13	5	-	3-5

Note: The dosing recommendations were calculated to achieve a steady state concentration of 1.5 ng/mL. The dosing recommendations by Nyberg (10-16 ug/kg/day in infants) and Neutze (18 ug/kg/day in 4-18 months; 12 ug/kg/day in 18 months-17 years) et al are also similar to those calculated based on Suematsu data.

For more details please refer to Appendix D.

C. Intrinsic Factors

1. What is the influence of heart failure, renal failure and hepatic condition on the pharmacokinetics of digoxin?

Heart failure:

Studies of the absorption of digoxin in heart failure patients have produced differing results. Some studies have indicated no effect on the absorption of digoxin while other studies have reported that peak concentrations were lower and time to reach maximum peak serum concentrations were longer[48-50].

However, the extent of absorption is the same in congestive heart failure as in healthy volunteers. In children with congestive heart failure, the clearance of digoxin was significantly lower in all age groups as shown below.

Age	*Clearance (CL, L/day)*	
	With CHF	*Without CHF*
	Mean ± SD	Mean ± SD
<4 months	38.35 ± 21.62	45.01 ± 22.43
4 months-3 years	87.73 ± 56.96	118.46 ± 51.15
>3 years	120.57 ± 11.12	170.95 ± 44.40

Renal failure:

In renal failure the volume of distribution of digoxin is reduced (370L vs 510 L) and elimination half-life is prolonged[51]. Acute reduction in renal function causes digitalis toxicity. The total body clearance decreases to 23-58 ml/min in patients with creatinine clearance values of < 10 ml/min[52].

Hepatic impairment

Hepatic impairment has no influence on the pharmacokinetics of digoxin.

2. Is there an influence of genetic polymorphism on the pharmacokinetics of digoxin?

The functional polymorphism of MDR-1 was studied to examine the correlation of MDR-1 genotype with intestinal digoxin uptake[53, 54]. Figure 12 shows the comparison of digoxin Cmax of seven volunteers that carried homozygously the T/T-allele and seven volunteers with the homozygous C/C genotype in exon 26. A mean difference of 38% in Cmax was observed between the two groups.

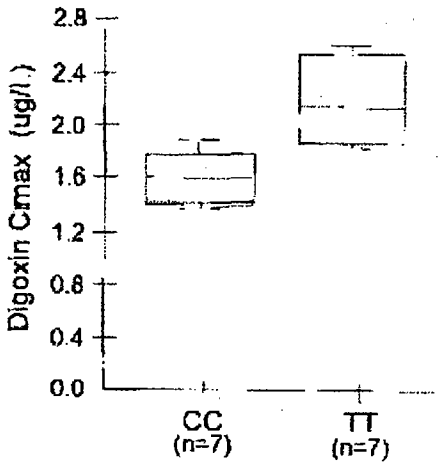


Figure 11. Correlation of MDR-1 genotype and digoxin uptake in vivo.

D. Extrinsic Factors

1. Is digoxin a substrate of P-glycoprotein?

MDR1/P-glycoprotein (P-gp), a member of the ATP-binding cassette (ABC) multidrug transporter superfamily, mediates active secretion of digoxin[55]. P-gp plays an important role in limiting the entry of xenobiotics into specific anatomic sites, such as the brain and gastrointestinal tract, and in facilitating the systemic removal of xenobiotics from the liver and the kidney (Figure 11). In the kidney, P-gp is expressed on the apical side of the proximal tubules, where it secretes

various drug substrates into the lumen. The observation that digoxin is actively secreted by the renal proximal tubules via P-gp is of particular importance for drug-drug interactions.

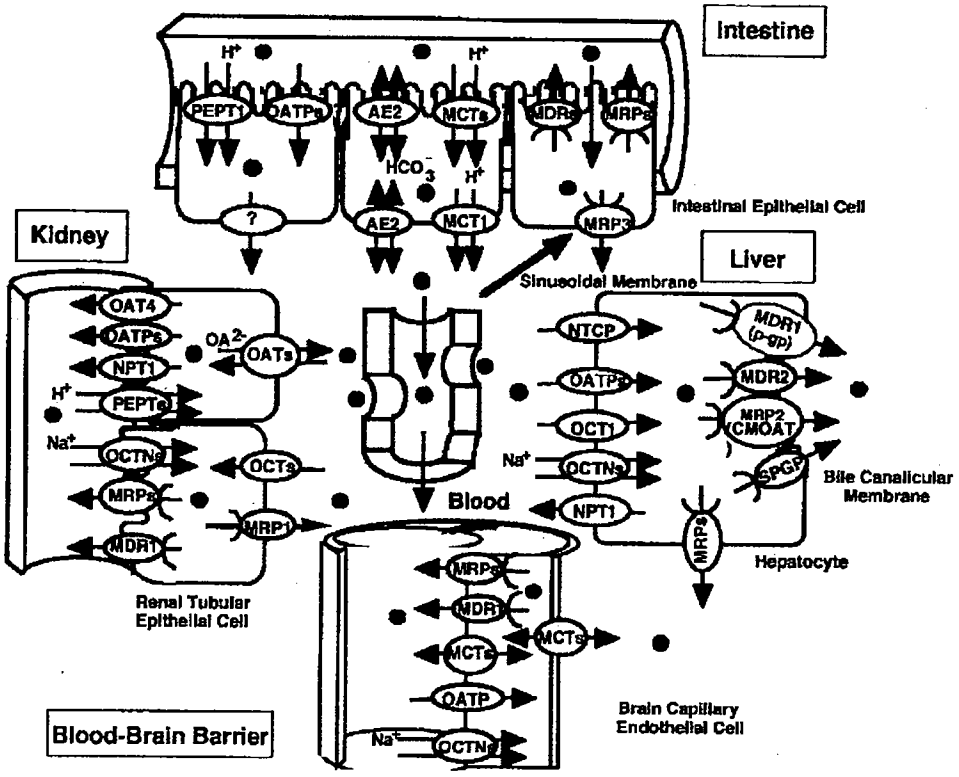


Figure 12. Human membrane transporters expressed in intestine, kidney, liver, blood- brain barrier.

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2. What is the current understanding of various drug-digoxin interactions?
The various reported drug interactions of digoxin as found in literature and as reported in PDR (Physician Desk Reference) are summarized.

Activated Charcoal[56]: Ten healthy subjects received infusions of 10 micrograms/kg digoxin alone and with 225 gm activated charcoal over 40 hours. Multiple serum digoxin concentration determinations were made after each dose by radioimmunoassay. Noncompartmental kinetic analysis was used. Digoxin clearance increased an average of 47% (range -2% to 119%) during charcoal treatment, from 12.2 +/- 2.0 to 18.0 +/- 2.9 L/hr. The volume of distribution at steady state decreased from 495 +/- 196 to 375 +/- 162 L, and the terminal t1/2 was shortened from 36.5 +/- 11.8 to 21.5 +/- 6.5 hr during charcoal treatment. Likewise, mean residence time decreased, from 41.1 +/- 20 to 19.9 +/- 7.8 hr. Kinetic predictions would suggest greater proportional increases in digoxin clearance in patients with renal impairment. Repeated doses of charcoal enhance the clearance of digoxin and should be considered for use in digoxin toxicity.

Adenosine[57]: Rarely, ventricular fibrillation has been reported following adenosine administration, including both resuscitated and fatal events. In most instances, these cases were associated with the concomitant use of **digoxin** and, less frequently with **digoxin** and verapamil. Although no causal relationship or drug-drug interaction has been established, adenosine should be used with caution in patients receiving **digoxin** or **digoxin** and verapamil in combination. Appropriate resuscitative measures should be available.

Acarbose[57]: Acarbose has been shown to change the bioavailability of **digoxin** when they are co-administered, which may require **digoxin** dose adjustment.
Acarbose may affect **digoxin** bioavailability and may require dose adjustment of **digoxin** by 16% (90% confidence interval: 8-23%), decrease mean C_{max} of

digoxin by 26% (90% confidence interval: 16-34%) and decreases mean trough concentrations of **digoxin** by 9% (90% confidence limit: 19% decrease to 2% increase).

Acitretin[57]: No significant pharmacokinetic interactions.

Albuterol Sulfate[57]: Mean decreases of 16% to 22% in serum **digoxin** levels were demonstrated after single dose intravenous and oral administration of albuterol, respectively, to normal volunteers who had received **digoxin** for 10 days. The clinical significance of these findings for patients with obstructive airway disease who are receiving albuterol and **digoxin** on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum **digoxin** levels in patients who are currently receiving **digoxin** and albuterol.

Alfuzosin[57]: Repeated co-administration of alfuzosin 10 mg tablets and **digoxin** 0.25 mg/day for 7 days did not influence the steady-state pharmacokinetics of either drug.

Alprazolam[58, 59]: Eight healthy men received a single, 1.25 mg dose of digoxin on two occasions, once in an otherwise drug-free control state and again while concurrently receiving alprazolam, 1.5 mg/day. There was no significant difference between control and alprazolam conditions in digoxin volume of distribution (11.0 vs. 11.2 L/kg), elimination t1/2 (46 vs. 41 hours), or total clearance from serum (2.8 vs. 3.6 ml/min/kg). Alprazolam coadministration slightly reduced mean 96-hour urinary excretion of digoxin (37.6% vs. 30.9% of dose; P less than 0.01), but there was no significant difference between treatment conditions in projected total cumulative excretion of digoxin (45.2% vs. 40.9% of dose) or in renal clearance of digoxin (1.23 vs. 1.44 ml/min/kg). Creatinine clearance also did not differ between the control and alprazolam conditions (164 vs. 142 ml/min). Thus therapeutic doses of alprazolam do not significantly alter digoxin clearance in healthy man.

Twelve inpatients receiving long-term digoxin (0.25 mg daily) randomly received oral administration of either 1.0 or 0.5 mg alprazolam per day for 7 days. In each dosage group, three patients were older than and three were younger than 65 years of age. The area under the concentration-time curve for serum digoxin increased significantly in patients receiving 1 mg alprazolam daily, and this increase was more pronounced in patients older than 65 years of age. Clinical digoxin toxicity developed in one elderly patient who was receiving 1 mg/day alprazolam.

Amiodarone Hydrochloride[57]: In patients receiving **digoxin** therapy, administration of oral amiodarone regularly results in an increase in the serum **digoxin** concentration that may reach toxic levels with resultant clinical toxicity. Amiodarone taken concomitantly with **digoxin** increases the serum **digoxin** concentration by 70% after one day. On initiation of oral amiodarone, the need for digitalis therapy should be reviewed and the dose reduced by approximately 50% or discontinued. If digitalis treatment is continued, serum levels should be closely monitored and patients observed for clinical evidence of toxicity.

Aminosalicylic Acid[57]: In one literature report 8 hours after the last dosage of aminosalicylic acid at 2 gm qid serum **digoxin** levels were reduced 40% in two of ten patients but not changed in the remaining eight.

Amlodipine besylate[57]: Co-administration of amlodipine with **digoxin** did not change serum **digoxin** levels or **digoxin** renal clearance in normal volunteers.

Aprepitant[57]: No significant pharmacokinetic interaction.

Argatroban[57]: In 12 healthy volunteers, intravenous infusion of argatroban (2 mcg/kg/min) over 5 days (study days 11 to 15) did not affect the steady-state pharmacokinetics of oral **digoxin** (0.375 mg daily for 15 days).

Aspirin[60]: The kinetics of digoxin-aspirin combination was studied in 8 healthy volunteers. In each subject, the kinetic parameters of digoxin after a single 1 mg intravenous dose were determined in the presence and absence of concurrent oral aspirin. During the digoxin with aspirin phsae of the study, 975 mg aspirin was taken orally three times daily. Aspirin was started three days before digoxin and was continued during the 5 days after digoxin. Aspirin induced no change in total body clearance, volume of distribution of digoxin.

Atorvastatin Calcium[57]: When multiple doses of atorvastatin and **digoxin** were coadministered, steady-state plasma **digoxin** concentrations increased by approximately 20%. Patients taking **digoxin** should be monitored appropriately.

Azithromycin[57]: Elevated **digoxin** levels.

Benazepril hydrochloride[57]: Benazepril has been used concomitantly with **digoxin** without evidence of clinically important adverse interactions.

Bisoprolol[57]: No significant pharmacokinetic interactions.

Bosentan[57]: No significant pharmacokinetic interactions.

Candesartan Cilexetil[57]: No significant pharmacokinetic interactions.

Captopril[57]: In a study of young healthy male subjects no evidence of a direct pharmacokinetic captopril **digoxin** interaction could be found.
The effects of captopril on serum digoxin concentrations were studied in 8 patients with severe (NYHA Class IV) congestive heart failure[61]. Serum digoxin concentrations were determined before and after the administration of captopril for 1 week in patients on chronic digoxin therapy. Each patient who was taking 0.25 mg of digoxin PO q.d., was administered 12.5 mg of captopril PO t.i.d. for 7

days. The peak serum concentration of digoxin (Cmax) before and after (on Days 0 and 7) captopril administration was 1.7+/-0.2 ng/ml and 2.7+/-0.2 ng/ml, the time to peak (tmax) was 2.4+/-0.5 h and 1.3+/-0.2 h, and the area under the 24-hour digoxin concentration-time curve (AUC0-24h) was 30.0+/-1.5 ng x h/ml and 41.7+/-3.4 ng x h/ml, respectively. While captopril caused a significant increase in peak serum concentration and the area under the digoxin concentration-time curve, it decreased the time to digoxin peak ($p = 0.01$, $p = 0.04$, $p = 0.01$, respectively). No patient developed evidence of digoxin toxicity. Concomitant administration of captopril with digoxin increases serum digoxin concentration in patients with severe congestive heart failure.

Carvedilol[57]: Following concomitant administration of carvedilol (25 mg once daily) and **digoxin** (0.25 mg once daily) for 14 days, steady-state AUC and trough concentrations of **digoxin** were increased by 14% and 16%, respectively, in 12 hypertensive patients.
Both **digoxin** and carvedilol slow AV conduction. Therefore, increased monitoring of **digoxin** is recommended when initiating, adjusting, or discontinuing carvedilol.

Cholesytramine[62-64]: Absorption of digoxin reduced by 30-40%. Cholestyramine's reduction of digoxin oral bioavailability is related to the dose of cholestyramine and the proximity of the time of administration of the two drugs.

Citalopram Hydrobromide[57]: In subjects who had received 21 days of 40 mg/day citalopram, combined administration of citalopram and **digoxin** (single dose of 1 mg) did not significantly affect the pharmacokinetics of either citalopram or **digoxin**.

Clarithromycin[57]: Elevated **digoxin** serum concentrations in patients receiving clarithromycin and **digoxin** concomitantly have also been reported in post-marketing surveillance. Some patients have shown clinical signs consistent

with **digoxin** toxicity, including potentially fatal arrhythmias. Serum **digoxin** levels should be carefully monitored while patients are receiving **digoxin** and clarithromycin simultaneously.

In a randomized, placebo-controlled, double-blind cross-over design single oral doses of 0.75 mg digoxin with oral coadministration of placebo or 250 mg clarithromycin twice daily for 3 days were administered to 12 healthy men[65]. Additionally, three of the subjects received single intravenous doses of 0.01 mg kg^{1} digoxin with oral placebo or clarithromycin.

Oral coadministration of clarithromycin resulted in a 1.7-fold increase of the area under the digoxin plasma concentration-time curve [mean AUC(0,24) ± SD 23 ± 5.2 *vs.* 14 ± 2.9 µg L^{-1} h; 95% confidence interval (CI) on the difference 7.0, 12; *P*= 0.002] and in a reduction of the nonglomerular renal clearance of digoxin [mean Cl_{Rng}(0, 24) ± SD 34 ± 39 *vs.* 57 ± 41 mL min^{1}; 95% CI on the difference 7.2, 45; *P* = 0.03]. The ratios of mean digoxin plasma concentrations with and without clarithromycin were highest during the absorption period of clarithromycin. After intravenous administration digoxin AUC(0,24) increased only 1.2-fold during coadministration of clarithromycin.

Increased oral bioavailability and reduced nonglomerular renal clearance of digoxin both contribute to the interaction between digoxin and clarithromycin, probably due to inhibition of intestinal and renal P-glycoprotein.

Clopidogrel[57]: No significant pharmacokinetic interaction.

Colesevelam[57]: No significant pharmacokinetic interaction.

Colestipol Hydrochloride[57]: Particular caution should be observed with digitalis preparations since there are conflicting results for the effect of colestipol hydrochloride on the availability of **digoxin** and digitoxin. The potential for binding of these drugs if given concomitantly is present. Discontinuing colestipol hydrochloride could pose a hazard to health if a potentially toxic drug that is

significantly bound to the resin has been titrated to a maintenance level while the patient was taking colestipol hydrochloride.

Cyclosporine[57]: Reduced clearance of **digoxin** has been observed when these drugs are administered with cyclosporine. In addition, a decrease in the apparent volume of distribution of **digoxin** has been reported after cyclosporine administration. Severe digitalis toxicity has been seen within days of starting cyclosporine in several patients taking **digoxin**.

Dalfopristin, Quinupristin (Synercid)[57]: A drug interaction between **Synercid** and **digoxin** cannot be excluded but is unlikely to occur via CYP3A4 enzyme inhibition. **Synercid** has shown *in vitro* activity (MICs of 0.25 mcg/mL when tested on two strains) against *Eubacterium lentum.* **Digoxin** is metabolized in part by bacteria in the gut and as such, a drug interaction based on **Synercid's** inhibition of **digoxin**'s gut metabolism (by *Eubacterium lentum*) may be possible.

Diclofenac sodium[57]: Elevated **digoxin** levels have been reported in patients receiving **digoxin** and diclofenac sodium. Patients receiving **digoxin** and diclofenac sodium should be monitored for possible **digoxin** toxicity.

Dietary Fiber[66]: Sixteen healthy volunteers were regularly given 0.4 mg of digoxin daily as two capsules with breakfast. After ten days during which breakfast was supplemented with 11 g of bran fiber, steady-state predose mean serum digoxin was lower (0.89 +/- 0.19 versus 0.84 +/- 0.18 ng/mL, P less than .05) and mean 24-hour area under curve determination was lower (30.5 +/- 6.1 versus 28.4 +/- 6.0 ng X hr/mL, P less than .05) than during the control period without bran. Height and time of peak serum digoxin, and 24-hour urinary digoxin were not significantly different. The 6 to 7% reduction in digoxin absorption from capsules is less than that reported from tablets and is probably clinically unimportant.

Diltiazem[57]: Administration of diltiazem hydrochloride with **digoxin** in 24 healthy male subjects increased plasma **digoxin** concentrations approximately 20%. Another investigator found no increase in **digoxin** levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of **digoxin** levels, it is recommended that **digoxin** levels be monitored when initiating, adjusting, and discontinuing diltiazem hydrochloride therapy to avoid possible over- or under-digitalization.

Dipyridamole[67]: The effects of dipyridamole (300 mg/d for 3 days) versus placebo on the pharmacokinetics of single oral dose of digoxin (0.5 mg) were studied in 12 healthy subjects. A 20% and 13% increase in AUC0-4h and AUC0-24h of digoxin was observed during dipyridamole administration.

Disopyramide[68-71]: A prospective study was performed to compare the effects of disopyramide in patients receiving maintenance digoxin therapy. During the disopyramide treatment a small rise in serum digoxin was noted (mean 1.3 +/- 0.16 to 1.5 +/- 0.19 nmol/l, $P < 0.05$).

Dofetilide[57]: Studies in healthy volunteers have shown that dofetilide does not affect the pharmacokinetics of **digoxin**. In patients, the concomitant administration of **digoxin** with dofetilide was associated with a higher occurrence of torsade de pointes. It is not clear whether this represents an interaction with dofetilide or the presence of more severe structural heart disease in patients on **digoxin**; structural heart disease is a known risk factor for arrhythmia. No increase in mortality was observed in patients taking **digoxin** as concomitant medication.

Donepezil Hydrochloride[57]: No significant pharmacokinetic interaction. Donepezil did not effect the protein binding of digoxin.

Doxazosin Mesylate[57]: No effect on protein binding of digoxin.

Dutasteride[57]: In a study of 20 healthy volunteers, dutasteride did not alter the steady-state pharmacokinetics of **digoxin** when administered concomitantly at a dose of 0.5 mg/day for 3 weeks.

Enalapril Maleate[57]: Enalapril has been used concomitantly with **digoxin** without evidence of clinically significant adverse interactions.

Epoprostenol Sodium[57]: In a pharmacokinetic substudy in patients with congestive heart failure receiving **digoxin** in whom therapy with epoprostenol was initiated, apparent oral clearance values for **digoxin** (n = 30) were decreased by 13% and 15%, respectively, on the second day of therapy and had returned to baseline values by day 87. However, patients on **digoxin** may show elevations of **digoxin** concentrations after initiation of therapy with epoprostenol, which may be clinically significant in patients prone to **digoxin** toxicity.

Eprosartan[57]: Concomitant administration of eprosartan with **digoxin** had no effect on a single oral-dose **digoxin** pharmacokinetics.

Ertapenem[57]: *In vitro* studies indicate that ertapenem does not inhibit P-glycoprotein-mediated transport of **digoxin**.

Erythromycin[57]: Concomitant administration of erythromycin and **digoxin** has been reported to result in elevated **digoxin** serum levels.

Escitalopram Oxalate[57]: In subjects who had received 21 days of 40 mg/day racemic citalopram, combined administration of citalopram and **digoxin** (single dose of 1 mg) did not significantly affect the pharmacokinetics of **digoxin**.

Esmolol[57]: When **digoxin** and esmolol were concomitantly administered intravenously to normal volunteers, there was a 10-20% increase in **digoxin** blood levels at some time points.

Esomeprazole[57]: Esomeprazole inhibits gastric acid secretion. Therefore, esomeprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g., **digoxin**).

Ezetimibe[57]: Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on the bioavailability of **digoxin** and the ECG parameters (HR, PR, QT, and QTc intervals) in a study of twelve healthy adult males.

Famciclovir[57]: The steady-state pharmacokinetics of **digoxin** were not altered by concomitant administration of multiple doses of famciclovir (500 mg t.i.d.).

Felodipine[57]: When given concomitantly with felodipine ER, the pharmacokinetics of **digoxin** in patients with heart failure were not significantly altered.

Finasteride[57]: No clinically meaningful interactions.

Flecainide Acetate[57]: During administration of multiple oral doses of flecainide to healthy subjects stabilized on a maintenance dose of **digoxin,** a 13%-19% increase in plasma **digoxin** levels occurred at six hours postdose. Flecainide has been administered to patients receiving **digitalis** preparations without adverse effects.

Fluvastatin Sodium[57]: In a crossover study involving 18 patients chronically receiving **digoxin**, a single 40 mg dose of immediate release fluvastatin had no

effect on **digoxin** AUC, but had an 11% increase in **digoxin** C_{max} and small increase in **digoxin** urinary clearance.

Fondaparinux Sodium[57]: In clinical studies performed with fondaparinux, the concomitant use of oral anticoagulants (warfarin), platelet inhibitors (acetylsalicylic acid), NSAIDs (piroxicam), and **digoxin** did not significantly affect the pharmacokinetics/pharmacodynamics of fondaparinux sodium. In addition, fondaparinux neither influenced the pharmacodynamics of warfarin, acetylsalicylic acid, piroxicam, and **digoxin**, nor the pharmacokinetics of **digoxin** at steady state.

Foscarnet[57]: Physical incompatibility has been reported with digoxin. Digoxin should not be administered concurrently via the same catheter.

Galantamine Hydrobromide[57]: Galantamine at 24 mg/day had no effect on the steady-state pharmacokinetics of **digoxin** (0.375 mg once daily) when they were coadministered. In this study, however, one healthy subject was hospitalized for 2 nd and 3 rd degree heart block and bradycardia.

Gatifloxacin[57]: Overall, only modest increases in C_{max} and AUC of **digoxin** were noted (12% and 19% respectively) in 8 of 11 healthy volunteers who received concomitant administration of gatifloxacin (400 mg oral tablet, once daily for 7 days) and **digoxin** (0.25 mg orally, once daily for 7 days). In 3 of 11 subjects, however, a significant increase in **digoxin** concentrations was observed. In these 3 subjects, **digoxin** C_{max} increased by 18%, 29%, and 58% while **digoxin** AUC increased by 66%, 104%, and 79%, and **digoxin** clearance decreased by 40%, 51%, and 45%. Although dose adjustments for **digoxin** are not warranted with initiation of gatifloxacin treatment, patients taking **digoxin** should be monitored for signs and/or symptoms of toxicity. In patients who display signs and/or symptoms of **digoxin** intoxication, serum **digoxin**

concentrations should be determined, and **digoxin** dosage should be adjusted as appropriate.

Gemifloxacin Mesylate[57]: Gemifloxacin 320 mg at steady-state did not affect the repeat dose pharmacokinetics of **digoxin** (0.25 mg once daily to healthy elderly subjects).

Grapefruit Juice[72, 73]: Twelve healthy volunteers participated in this open randomized crossover study comparing the effect of grapefruit juice consumption (versus water) on the pharmacokinetics of a single oral dose of digoxin (0.5 mg). After an overnight fast, subjects ingested 220 mL of water or grapefruit juice 30 minutes before administration of digoxin and 3.5, 7.5 and 11.5 hours after digoxin dose. Digoxin was ingested with 50 mL of water or grapefruit juice, depending on the study period. Grapefruit juice had no significant effect on the maximum plasma drug concentration (C(max)) of digoxin or the area under the plasma concentration-time curve (AUC) from time zero to 48 hours. However, there was a 9% increase in the digoxin AUC from time zero to 4 hours and from time zero to 24 hours (P =.01) during grapefruit juice administration. The digoxin renal clearance remained unchanged during both periods. No significant interactions between digoxin and grapefruit juice have been reported in other studies also.

Indomethacin[57]: Indomethacin given concomitantly with **digoxin** has been reported to increase the serum concentration and prolong the half-life of **digoxin**. Therefore, when indomethacin and **digoxin** are used concomitantly, serum **digoxin** levels should be closely monitored.

Irbesartan[57]: No significant drug-drug pharmacokinetic interactions have been found in interaction studies with **digoxin**.

Isradipine[57]: The concomitant administration of immediate-release isradipine and **digoxin** in a single-dose pharmacokinetic study did not affect renal, non-renal and total body clearance of **digoxin**.

Itraconazole[57]: Concomitant administration of **digoxin** and itraconazole has led to increased plasma concentrations of **digoxin.**

Ketoconazole[57]: Rare cases of elevated plasma concentrations of **digoxin** have been reported. It is not clear whether this was due to the combination of therapy. It is, therefore, advisable to monitor **digoxin** concentrations in patients receiving ketoconazole.

Ketorolac Tromethamine[57]: Ketorolac does not alter **digoxin** protein binding.

Lansoprazole[57]: Lansoprazole causes a profound and long-lasting inhibition of gastric acid secretion; therefore, it is theoretically possible that lansoprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g., ketoconazole, ampicillin esters, iron salts, **digoxin**).

Levetiracetam[57]: Levetiracetam (1000 mg twice daily) did not influence the pharmacokinetics and pharmacodynamics (ECG) of **digoxin** given as a 0.25 mg dose every day.

Levofloxacin[57]: No significant effect of levofloxacin on the peak plasma concentrations, AUC, and other disposition parameters for **digoxin** was detected in a clinical study involving healthy volunteers.

Lisinopril[57]: No meaningful clinically important pharmacokinetic interactions occurred when lisinopril was used concomitantly with **digoxin.**

Losartan potassium[57]: Losartan did not affect the pharmacokinetics of oral or intravenous **digoxin.**

Lovastatin[57]: In patients with hypercholesterolemia, concomitant administration of lovastatin and **digoxin** resulted in no effect on **digoxin** plasma concentrations.

Magnesium-Aluminium Hydroxide/Kaolin-Pectin[74]: Twelve healthy fasting volunteers received two 0.2-mg digoxin capsules or tablets with 60 ml water, 60 ml Maalox, or 60 ml Kaopectate in a randomized, single-dose, six-way crossover study. Concentrations of digoxin in multiple plasma samples and in all urine collected during the 24 hours after each dose were determined by radioimmunoassay. Compared to the water treatment, administration of both tablets and capsules with Maalox or Kaopectate reduced the peak digoxin plasma concentrations but did not significantly influence the time of peak concentration. Neither Maalox nor Kaopectate influenced the area under the 24-hour plasma concentration--time curve for either tablets or capsules. However, 24-hour urinary recovery of digoxin from tablets tended to be reduced by Maalox and Kaopectate; this was not the case with capsules. Digoxin capsules may have an advantage over currently available tablets in clinical situations requiring digoxin coadministration with nonabsorbable gastrointestinal preparations.
The effect of a kaolin-pectin antidiarrheal mixture on steady-state plasma levels of orally administered digoxin in subjects receiving chronic digoxin therapy was evaluated when the antidiarrheal and the cardiac glycoside were given concomitantly and when two doses of antidiarrheal were given, one 2 hours before and the other 2 hours after digoxin[75]. Although simultaneous administration of both products decreased peak digoxin levels by 36 per cent, 24-hour areas under the curve were reduced by only 15 per cent, indicative of a slight decrease in digoxin bioavailability. In contrast, when their times of

administration were separated by 2 hours, no evidence of a drug interaction was noted.

Meloxicam[57]: Meloxicam 15 mg once daily for 7 days did not alter the plasma concentration profile of **digoxin** after (beta)-acetyldigoxin administration for 7 days at clinical doses. *In vitro* testing found no protein binding drug interaction between **digoxin** and meloxicam.

Metformin HCl[57]: Cationic drugs (e.g., **digoxin**) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems.

Metoclopramide[76]: Metoclopramide was administered to eleven patients, on maintanence digoxin therapy, in three daily doses of 10 mg for 10 days. Serum digoxin concentrations were measured on 8^{th}, 9^{th} and 10^{th} days 24 hours after digoxin administration. The mean initial serum digoxin concentration was 0.72 ng/mL. After addition of metoclopramide, the serum digoxin concentrations fell in all patients to 0.46 ng/mL. When metoclopramide was discontinued the serum digoxin returned to the original level, reach a mean of 0.75 ng/mL after 10 days.

Mexilitine Hydrochloride[57]: Mexilitine does not alter serum **digoxin** levels but magnesium-aluminum hydroxide, when used to treat gastrointestinal symptoms due to mexilitine, has been reported to lower serum **digoxin** levels.

Miglitol[57]: In a healthy volunteer study, co-administration of either 50 mg or 100 mg miglitol 3 times daily together with **digoxin** reduced the average plasma concentrations of **digoxin** by 19% and 28%, respectively. However, in diabetic patients under treatment with **digoxin**, plasma **digoxin** concentrations were not altered by co-administration of miglitol 100 mg 3 times daily × 14 days.

Moexipril Hydrochloride[57]: No clinically important pharmacokinetic interactions occurred when moexipril was administered concomitantly with **digoxin**.

Moricizine[77-80]: Potential interactions between moricizine (Ethmozine®) were studied in both normal volunteers and patients. In a study of digoxin pharmacokinetics after single intravenous dose, no differences were found between values at baseline and those noted after steady-state administration of moricizine (12 mg/kg/day in 3 divided doses). Coadministrations of digoxin and moricizine caused a significant increase in PR intervals. In a study of moricizine efficacy for suppression of chronic ventricular ectopy in patients concomitantly receiving digoxin (for congestive heart failure or atrial fibrillation), digoxin concentrations were measured before, during and after 2 weeks of treatment with moricizine (approximately 10 mg/kg/day in divided doses). No significant changes in digoxin concentrations were observed.
Moricizine frequently increases the PR interval and QRS duration, and there are reports of first-degree atrioventricular block or bundle branch block developing in patients during concomitant digitalis administration. The known effects of moricizine on calcium conductance may explain the effects on atrioventricular node conduction.

Moxifloxacin[57]: No significant effect of moxifloxacin (400 mg once daily for two days) on (0.6 mg as a single dose) AUC was detected in a study involving 12 healthy volunteers. The mean C_{max} increased by about 50% during the distribution phase of digoxin. This transient increase in **digoxin** C_{max} is not viewed to be clinically significant.

Montelukast sodium[57]: No significant pharmacokinetic interactions.

Mycophenolate mofetil[57]: Mycophenolate at concentrations as high as 100 µg/mL had little effect on the binding of **digoxin.**

Nateglinide[57]: When nateglinide 120 mg before meals was administered in combination with a single 1-mg dose of **digoxin** to healthy volunteers, there were no clinically relevant changes in the pharmacokinetics of either agent.

Neomycin[81]: The effect of the administration of the antibiotic neomycin sulfate on the absorption of digoxin was assessed in crossover studies in normal human volunteers. Doses of neomycin (1 and 3 g) markedly depressed serum digoxin concentrations, the areas under the serum concentration-time curves, and cumulative 6-day urinary digoxin excretion after the oral ingestion of 0.5 mg of the cardiac glycoside in tablet form. Neomycin also prolonged the mean time at which peak serum digoxin levels were attained by 1.7 to 3 hr. The inhibition of digoxin absorption was also seen: (1) when the antibiotic was given 3 or 6 hr before the cardiac glycoside, (2) with digoxin tablets of varying dissolution rate, (3) when digoxin or neomycin solutions were used instead of tablets, and (4) in a patient who had had a total gastrectomy. When neomycin was administered with maintenance doses of digoxin, steady state serum digoxin concentrations were significantly reduced. When neomycin was given after a 9-day period of digitalization, the terminal serum digoxin half-life was not significantly shortened. In vitro, neomycin did not affect the movement of digoxin across dialysis membranes, nor did it precipitate digoxin out of human bile or intestinal fluid. Neomycin thus clearly depresses the rate and extent of digoxin absorption in man.

Nesiritide[57]: During clinical studies, nesiritide was administered concomitantly with other medications, including: diuretics, **digoxin**, oral ACE inhibitors, anticoagulants, oral nitrates, statins, class III antiarrhythmic agents, beta-blockers, dobutamine, calcium channel blockers, angiotensin II receptor antagonists, and dopamine. Although no PK interactions were specifically assessed, there did not appear to be evidence suggesting any clinically significant PK interaction.

Nicardipine Hydrochloride[57]: Studies have shown that nicardipine capsules usually do not alter **digoxin** plasma concentrations. However, as a precaution, **digoxin** levels should be evaluated when concomitant therapy with nicardipine intravenous is initiated.

Twenty patients in a stable condition suffering from congestive heart failure were treated with digoxin for at least three weeks and then with nicardipine concomitantly for five days[82]. No statistically significant variation in serum digoxin concentrations determined at seven control times during a 24-hour period or in its mean concentration was found in the two groups of values examined before and after the concurrent nicardipine treatment. The mean increase of 6.8% in the AUC0-24h was not significant either. Since the maximum increase in serum digoxin concentrations at the steady state never exceeded 0.5 ng/ml, a toxic effect is not likely to occur in patients whose digoxin levels are normally monitored.

Nifedipine[57]: Administration of nifedipine with **digoxin** increased **digoxin** levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in **digoxin** levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which **digoxin** blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated **digoxin** levels, it is recommended that **digoxin** levels be monitored when initiating, adjusting, and discontinuing nifedipine to avoid possible over- or under-digitalization.

Nisoldipine[57]: No significant pharmacokinetic interactions.

Nitrendipine[83]: The effect of nitrendipine in two different dosages on digoxin plasma levels, urinary recovery, and systolic time intervals was investigated in

eight healthy volunteers. Following an adequate loading dose of the glycoside, 0.25 mg digoxin twice daily was given alone for 2 weeks orally. After that, 0.25 mg digoxin twice daily was administered for two 1-week periods combined with nitrendipine, 10 mg or 20 mg once daily. The study was completed with a second digoxin monotherapy phase lasting seven days. Nitrendipine, 20 mg daily, led to a significant increase of the digoxin plasma concentration and of its area under the plasma concentration-time curve (AUC0-12) compared with digoxin monotherapy. Thus, AUC0-12 was 9.7 +/- 0.75 ng ml-1 h (X +/- SEM) when digoxin was given alone and was 11.2 +/- 0.92 ng ml-1 h under coadministration of the calcium antagonist (p less than 0.05). Nitrendipine in the dosage of 10 mg once daily caused a small, insignificant tendency to elevate digoxin plasma levels (Digoxin alone: 1.34±0.16 ng/mL vs Digoxin+10 mg nitrendipine: 1.64±0.24 ng/mL). In conclusion, nitrendipine, 20 mg daily, causes a significant increase of digoxin plasma concentration (1.34±0.16 vs 2.10±0.24 ng/mL) and of its AUC (9.7±0.75 vs 11.2±0.93 $ng.mL^{-1}.h$).

Olmesartan Medoxomil[57]: No significant pharmacokinetic interactions.

Omeprazole[84]: In a randomized two-way crossover design a single dose of 1 mg digoxin was administered either alone (control) or on day 8 of an 11 day course of omeprazole 20 mg once daily. On average, Cmax and AUC values for digoxin were approximately 10% higher and tmax tended to be shorter during the administration of omeprazole, while the elimination rate constant was unaffected. The increase in AUC(0,96 h) was statistically significant ($p<0.05$), but within the accepted range for bioequivalence. In two subjects the increase was approximately 30%. It is concluded that co-treatment with omeprazole causes a minor increase in the absorption of oral digoxin. The magnitude of this effect is not considered to be clinically relevant for the majority of patients.

Orlistat[57]: In 12 normal-weight subjects receiving orlistat 120 mg three times a

day for 6 days, orlistat did not alter the pharmacokinetics of a single dose of **digoxin**

Pantoprazole Sodium[57]: No clinically relevant interactions.

Paroxetine Hydrochloride[57]: The steady-state pharmacokinetics of paroxetine was not altered when administered with **digoxin** at steady state. Mean **digoxin** AUC at steady state decreased by 15% in the presence of paroxetine. Since there is little clinical experience, the concurrent administration of paroxetine and **digoxin** should be undertaken with caution.

Perindopril Erbumine[57]: A controlled pharmacokinetic study has shown no effect on plasma **digoxin** concentrations when coadministered with perindopril tablets.

Pioglitazone Hydrochloride[57]: Co-administration of pioglitazone with 0.25 mg **digoxin** administered orally once daily for 7 days did not alter the steady-state pharmacokinetics of **digoxin.**

Pravastatin Sodium[57]: In a crossover trial involving 18 healthy male subjects given 20 mg pravastatin and 0.2 mg **digoxin** concurrently for 9 days, the bioavailability parameters of **digoxin** were not affected.

Prazosin[57]: Prazosin hydrochloride has been administered without any adverse drug interaction in limited clinical experience to date with cardiac glycosides--digitalis and **digoxin.**

Procainamide[70]: The effect of procainamide on digoxin serum concentrations was studied in 22 patients. All patients were at steady state for digoxin, defined as at least 7 days of continuous oral digoxin therapy (Lanoxin®, 0.25 mg). No

significant changes in digoxin serum concentration (16-22h sample) and PR intervals were observed.

Propafenone hydrochloride[57]: Propafenone produces dose-related increases in serum **digoxin** levels ranging from about 35% at 450 mg/day to 85% at 900 mg/day of propafenone without affecting **digoxin** renal clearance. These elevations of **digoxin** levels were maintained for up to 16 months during concomitant administration. Plasma **digoxin** levels of patients on concomitant therapy should be measured, and **digoxin** dosage should ordinarily be reduced when propafenone is started, especially if a relatively large **digoxin** dose is used or if plasma concentrations are relatively high.

Propantheline bromide[76, 85]. The effect of propantheline was studied in 18 healthy volunteers. The subjects were administered either two 0.25 mg digoxin tablets or two 0.20 mg digoxin capsules administered alone, with propantheline, 15 mg qid. The AUC0-24 (ng*h/mL) for tablets alone and with propantheline were 32.8 ± 12.3 and 40.6 ± 13.9 respectively. The AUC0-24 (ng*h/mL) for capsules alone and with propantheline were 31.7 ± 12.3 and 35.9 ± 12.9 respectively. The trough concentrations (ng/mL) for tablets alone and with propantheline were 0.88 ± 0.47 and 1.09 ± 0.35 respectively. The trough concentrations for capsules alone and with propantheline were 0.77 ± 0.28 and 0.96 ± 0.48 respectively.

In another study, 8 healthy volunteers received 0.50 mg digoxin in tablet or liquid form. One the second occasion, at least a week later, 30 mg propantheline was administered 30 minutes before administration of digoxin. It was observed that absorption of digoxin from tablet but not liquid formulation was affected by propantheline.

Quinapril[57]: No significant pharmacokinetic interactions.

Quinidine[70, 86-88]: The effect of quinidine on digoxin serum concentrations was studied in 22 patients. All patients were at steady state for digoxin, defined as at least 7 days of continuous oral digoxin therapy (Lanoxin®, 0.25 mg). Quinidine increased digoxin concentrations (16-22h sample) by 0.5 nmol/L in 21 of 22 patients. Anorexia, nausea and vomiting developed soon after starting the quinidine therapy in 10 of 22 patients. Quinidine prolonged the PR interval from 160 ± 14 ms to 183 ± 26 msNo significant changes in digoxin serum concentration and PR intervals were observed.

The mechanism by which quinidine increases the serum concentrations of digoxin is by interfering with renal and non-renal clearance of digoxin. The dose of digoxin should be adjusted during concomitant treatment with quinidine.

Quinine[89]: Quinine (250 mg/day) increased mean plasma digoxin concentration from 0.64 +/- 0.12 to 0.80 +/- 0.18 ng/ml (p less than 0.05) within one week. Urinary digoxin recovery rose from 154.0 +/- 18.8 to 181.5 +/- 22.6 micrograms/24 h (p less than 0.01), whereas renal digoxin clearance was unaltered in the presence of quinine (181.5 +/- 24.2 vs. 174.1 +/- 26.5 ml/min). An increase in quinine dose (to 750 mg/day) caused further increments in plasma digoxin levels, whereas renal digoxin clearance remained unchanged. Quinine elevates plasma digoxin concentrations in a stepwise fashion probably due to an impairment of extrarenal digoxin clearance.

Rabeprazole sodium[57]: Rabeprazole produces sustained inhibition of gastric acid secretion. An interaction with compounds which are dependent on gastric pH for absorption may occur due to the magnitude of acid suppression observed with rabeprazole. In normal subjects, co-administration of rabeprazole 20 mg QD resulted in increases in the AUC and C_{max} for **digoxin** of 19% and 29%, respectively. Therefore, patients may need to be monitored when such drugs are taken concomitantly with rabeprazole.

Raloxifene Hydrochloride[57]: Raloxifene has no effect on the pharmacokinetics of **digoxin.**

Ramipril[57]: No interactions with digoxin have been observed.

Repaglinide[57]: No significant pharmacokinetic interaction.

Rifampin[90]**:** Rifampicin reduced the oral bioavailability of digoxin from 63% to 44% in healthy volunteers mainly by inducing P-glycoprotein in the small intestine. The intestinal expression of the levels of P-glycoprotein correlated inversely with the AUC of oral digoxin.

Rivastigmine Tartarate[57]: No significant pharmacokinetic interaction.

Rofecoxib[57]: Rofecoxib 75 mg once daily for 11 days does not alter the plasma concentration profile or renal elimination of **digoxin** after a single 0.5 mg oral dose.

Ropinirole Hydrochloride[57]: Co-administration of ropinirole (2.0 mg t.i.d.) with **digoxin** (0.125-0.25 mg q.d.) did not alter the steady-state pharmacokinetics of **digoxin** in 10 patients.

Rosiglitazone maleate[57]: Repeat oral dosing of rosiglitazone (8 mg once daily) for 14 days did not alter the steady-state pharmacokinetics of **digoxin** (0.375 mg once daily) in healthy volunteers.

Rosuvastatin[91]: The effect of rosuvastatin on the pharmacokinetics of digoxin was assessed in 18 healthy male volunteers in this double-blind, randomized, two-way crossover trial. Volunteers were dosed with rosuvastatin (40 mg once daily) or placebo to steady state before being given a single dose of digoxin 0.5 mg. dosing. The geometric least square mean AUC(0-t) and Cmax of digoxin

were only 4% higher when the drug was coadministered with rosuvastatin compared to placebo. The 90% CIs for both treatment ratios (AUC(0-t) = 0.88-1.24; Cmax = 0.89-1.22) fell within the prespecified margin of 0.74 to 1.35; therefore, no significant pharmacokinetic interaction occurred between rosuvastatin and digoxin.

Salbutamol[92]: A single dose of the beta 2-adrenoceptor agonist salbutamol has previously been shown to decrease serum digoxin concentration in healthy volunteers. A possible explanation of the phenomenon is a beta 2-adrenoceptor-mediated increase in the specific binding of digoxin to skeletal muscle. The present study was undertaken to further elucidate the effect of salbutamol on the pharmacokinetics of digoxin in man. Nine volunteers were studied on two occasions during salbutamol or placebo treatment. On test days salbutamol, 4 micrograms.$kg^{-1}.h^{-1}$ or saline was infused for 10 h, preceded and followed by four and three days, respectively, of oral administration. A single i.v. injection of digoxin 15 micrograms.kg-1, was given 20 min after starting the infusion. At the end of the infusion a muscle biopsy was taken from the vastus lateralis. Blood samples for the analysis of serum digoxin and potassium were repeatedly taken over 72 h. Urine was collected over a period of 24 h for determination of the renal excretion of digoxin and potassium. The serum digoxin concentration, expressed as the AUC 0-6 h was 15% lower during salbutamol infusion than during saline infusion. Salbutamol caused significantly faster elimination of digoxin from the central volume of distribution to deeper compartments. Salbutamol had no effect on the renal clearance of digoxin. The skeletal muscle digoxin concentration tended to be higher (48%) during salbutamol compared to placebo treatment. The serum potassium concentration was significantly lower after salbutamol compared to placebo, as was the rate of renal excretion of potassium.

Sertraline Hydrochloride[57]: In a placebo-controlled trial in normal volunteers, administration of sertraline for 17 days (including 200 mg/day for the last 10 days) did not change serum **digoxin** levels or **digoxin** renal clearance.

Sevelamer Hydrochloride[57]: In 19 healthy subjects receiving 6 sevelamer capsules three times a day with meals for 2 days, Renagel did not alter the pharmacokinetics of a single dose of **digoxin.**

Simvastatin[57]: Concomitant administration of a single dose of **digoxin** in healthy male volunteers receiving simvastatin resulted in a slight elevation (less than 0.3 ng/mL) in **digoxin** concentrations in plasma (as measured by a radioimmunoassay) compared to concomitant administration of placebo and **digoxin.** Patients taking **digoxin** should be monitored appropriately when simvastatin is initiated.

Sirolimus[57]: No clinically relevant interactions when 0.25 mg digoxin was administered daily for 8 days and a single 10-mg dose of sirolimus oral solution was given on day 8 to 24 healthy volunteers.

Spironolactone[93-95]: Spironolactone increases the plasma concentrations of digoxin by reducing the renal clearance via the inhibition of renal tubular secretion of the drug. Cardiac manifestations of digitalis toxicity resulting from pharmacokinetic interaction of spironolactone and digoxin may be modified by the suppressant effect of spironolactone upon digoxin induced arrhythmias.

St. John's Wort[96, 97]: In a clinical study, the administration of St. John's Wort extract to 8 healthy male volunteers during 14 days resulted in a 18% decrease in exposure after a single digoxin dose (0.5 mg), in 1.4 and 1.5 fold increased expressions of duodenal P-glycoprotein/MDR1 and CYP3A4 respectively.

Sucralfate[57]: Some studies have shown that simultaneous sucralfate administration in healthy volunteers reduced the extent of absorption (bioavailability) of single doses of **digoxin.** The mechanism of these interactions

appears to be nonsystemic in nature, presumably resulting from sucralfate binding to the concomitant agent in the gastrointestinal tract. Dosing the concomitant medication 2 hours before sucralfate eliminated the interaction.

Sulfasalazine[57]: Reduced absorption of **digoxin** have been reported when those agents were administered concomitantly with sulfasalazine.
To determine whether or not SSA consistently interfered with the therapeutic effect of digoxin, both drugs were administered to 10 normal subjects in a crossover study[98]. Each received 2 doses of digoxin (0.5 mg, elixir): one dose given alone, and a second dose after 6 days of treatment with SSA. When digoxin was given with SSA, the average area under the serum digoxin curve fell from the control value of 8.79 ng-hr-ml(-1) to 6.66 ng-hr-ml(-1) (p less than 0.05), fell and total urinary excretion decreased from 278 µg/10 days to 228 µg/10 days ($p<0.025$). These changes suggest interference with the bioavailability of digoxin by SSA. Studies were conducted to determine whether SSA inhibited digoxin absorption by physically absorbing the glycoside from solution. In vitro tests failed to reveal any significant adsorptive properties for SSA.

Tamsulosin Hydrochloride[57]: In two studies in healthy volunteers (n=10 per study; age range 19-39 years) receiving tamsulosin capsules 0.4 mg/day for two days, followed by tamsulosin capsules 0.8 mg/day for five to eight days, single intravenous doses of **digoxin** 0.5 mg resulted in no change in the pharmacokinetics of **digoxin**. Therefore, dosage adjustments are not necessary when a tamsulosin capsule is administered concomitantly with **digoxin**.

Tegaserod Maleate[57]: A pharmacokinetic interaction study with **digoxin** demonstrated that concomitant administration of tegaserod reduced peak plasma concentration and exposure of **digoxin** by approximately 15%. This reduction of bioavailability is not considered clinically relevant. When tegaserod is co-administered with **digoxin** dose adjustment is unlikely to be required.

Telmisartan[57]: When telmisartan was coadministered with **digoxin**, median increases in **digoxin** peak plasma concentration (49%) and in trough concentration (20%) were observed. It is, therefore, recommended that **digoxin** levels be monitored when initiating, adjusting, and discontinuing telmisartan to avoid possible over- or under-digitalization.

Terbinafine[57]: No significant pharmacokinetic interaction.

Teriparatide[57]: In a study of 15 healthy people administered **digoxin** daily to steady state, a single teriparatide dose did not alter the effect of **digoxin** on the systolic time interval (from electrocardiographic Q-wave onset to aortic valve closure, a measure of **digoxin**'s calcium-mediated cardiac effect). However, sporadic case reports have suggested that hypercalcemia may predispose patients to digitalis toxicity. Because teriparatide transiently increases serum calcium, teriparatide should be used with caution in patients taking digitalis.

Tetracycline[99]: In approximately 10 per cent of patients given digoxin, substantial conversion of the drug to cardioinactive, reduced metabolites (digoxin reduction products, or DRPs) occurs. The site and clinical importance of this conversion is unknown. In four normal volunteers taking digoxin daily for four weeks, urinary excretion of DRPs was greatest after a poorly absorbed tablet was ingested, and least after intravenous administration, Stool cultures from subjects known to make DRPs in vivo ("excretors") converted digoxin to DRPs; cultures from nonexcretors did not. Three excretors were given tablets for 22 to 29 days. A five-day course of erythromycin or tetracycline, administered after a base-line period of 10 to 17 days, markedly reduced or eliminated DRP excretion in urine and stool. Serum digoxin concentrations rose as much as twofold after antibiotics were given. We conclude that in some persons digoxin is inactivated by gastrointestinal bacteria. Changes in the enteric flora may markedly alter the state of digitalization.

Tiagabine Hydrochloride[57]: Concomitant administration of tiagabine did not affect the steady-state pharmacokinetics of **digoxin** or the mean daily trough serum level of **digoxin**.

Ticlopidine Hydrochloride[57]: Coadministration of ticlopidine with **digoxin** resulted in a slight decrease (approximately 15%) in **digoxin** plasma levels. Little or no change in therapeutic efficacy of **digoxin** would be expected.

Topiramate[57]: In a single-dose study, serum **digoxin** AUC was decreased by 12% with concomitant topiramate administration. The clinical relevance of this observation has not been established.

Torsemide[57]: No effect on pharmacokinetics of digoxin.

Tramadol hydrochloride[57]: Post-marketing surveillance of tramadol has revealed rare reports of **digoxin** toxicity.

Trandolapril[57]: Trandolapril did not affect the plasma concentration (pre-dose and 2 hours post-dose) of oral **digoxin** (0.25 mg).

Triamterene[93]: Triamterene has been reported to reduce the non-renal clearance of digoxin by 20% without influencing its renal elimination.

Trovafloxacin Mesylate[57]: Trovafloxacin (200 mg p.o. daily for 10 days) co-administration with **digoxin** (0.25 mg daily for 20 days) did not significantly alter systemic exposure (AUC) to **digoxin** or the renal clearance of **digoxin**.

Valacyclovir Hydrochloride[57]: The pharmacokinetics of **digoxin** was not affected by coadministration of valacyclovir gram 3 times daily.

Valsartan[57]: No clinically significant pharmacokinetic interactions.

Verapamil Hydrochloride[57]: Clinical use of verapamil in digitalized patients has shown the combination to be well tolerated if **digoxin** doses are properly adjusted. However, chronic verapamil treatment can increase serum **digoxin** levels by 50% to 75% during the first week of therapy, and this can result in digitalis toxicity. In patients with hepatic cirrhosis the influence of verapamil on **digoxin** kinetics is magnified. Verapamil may reduce total body clearance and extrarenal clearance of digitoxin by 27% and 29%, respectively. Maintenance and digitalization doses should be reduced when verapamil is administered, and the patient should be reassessed to avoid over- to underdigitalization. Whenever overdigitalization is suspected, the daily dose of digitalis should be reduced or temporarily discontinued. On discontinuation of verapamil use, the patient should be reassessed to avoid underdigitalization. In previous clinical trials with other verapamil formulations related to the control of ventricular response in digitalized patients who had atrial fibrillation or atrial flutter, ventricular rates below 50/min at rest occurred in 15% of patients, and asymptomatic hypotension occurred in 5% of patients.

Voriconazole[57]: Voriconazole (200 mg Q12h × 12 days) had no significant effect on steady state C_{max} and AUC^{t} of **digoxin** (0.25 mg once daily for 10 days) in healthy subjects.

Zaleplon[57]: Zaleplon (10 mg) did not affect the pharmacokinetic or pharmacodynamic profile of **digoxin** (0.375 mg q24h for 8 days).

Zolpidem Tartarate[57]: No significant pharmacokinetic interactions.

Drug-Disease Interactions:

Certain disease conditions have been reported to alter the pharmacokinetics of digoxin. Some of them are summarized below:

Thyroid[100, 101]: The thyroid status in a individual has been reported to influence digoxinplasma concentrations by a change in volume of distribution, change in renal or non-renal excretion, changes in absorption characteristics. In patients with hypothyroidism, higher serum concentrations of digoxin have been observed. In patients with hyperthyroidism, decreased serum concentrations of digoxin have been reported.

In a more recent study, duodenal expression of P-glycoprotein has been studied in 8 healthy volunteers before and after coadministration with levothyroxine[102]. Duodenal MDR1 mRNA expression and immunoreactive P-glycoprotein were increased 1.4 fold and 3.8 fold, respectively, after administration of levothyroxine. This study indicates that expression of intestinal P-glycoprotein in humans is influenced by thyroid hormones. This could possibly explain the observed thyroid status-digoxin interactions.

Malabsorption Syndromes: Eleven patients with malabsorption syndrome (nine with malabsorption and two with maldigestion due to pancreatic insufficiency) were compared with a control group of 10 patients who had no intestinal disease[103]. The mean steady-state serum digoxin level after 0.25 mg dose for nine patients with malabsorption was significantly less than that for the control group ($p<0.001$) whereas levels for the two patients with pancreatic insufficiency were not significantly different from control values.

A case of malabsorption of digoxin from tablets, gel caps, and elixir in a patient with an end jejunostomy has been reported[104].

The relative steady-state bioavailability of two oral digoxin dosage forms was studied in 17 subjects with malabsorption syndromes[105]. Male subjects received the following treatments in randomized crossover fashion for 14 days: three 0.125-mg digoxin tablets or three 0.1-mg digoxin capsules once daily. Female subjects received digoxin on the same schedule but at two-thirds the dose. Serum and urine samples were collected and analyzed for digoxin by radioimmunoassay, and treatments were compared by evaluating

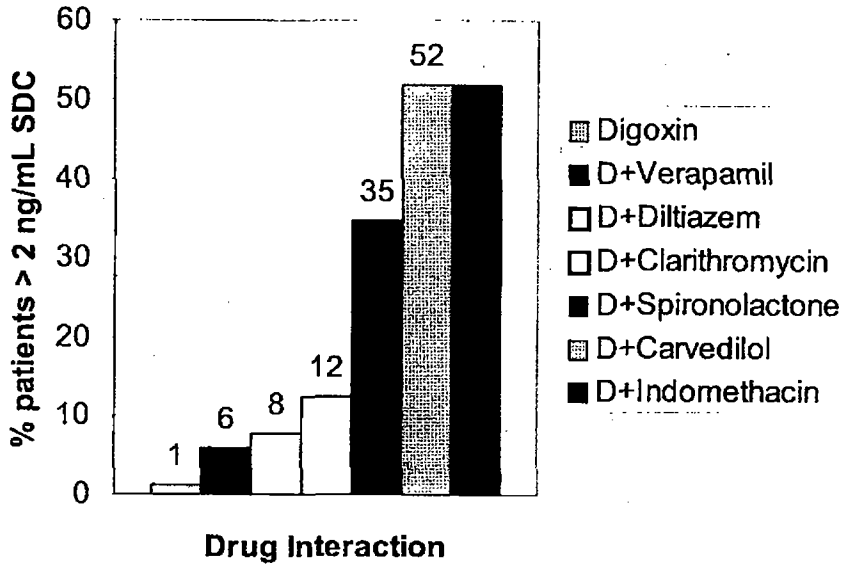
pharmacokinetic parameters. The mean area under the serum concentration versus time curve for tablets (28.1 h.nmol/L [21.9 h.ng/mL]) was smaller (p less than 0.03) than that for capsules (31.1 h.nmol/L [24.3 h.ng/mL]), and the mean maximum serum digoxin concentration for tablets (2.9 nmol/L [2.3 ng/mL]) was lower (p less than 0.02) than that for capsules (4.0 nmol/L [3.1 ng/mL]). There was no difference in cumulative urinary excretion of digoxin between the two treatments. It was concluded that digoxin from Lanoxin Tablets appears to be well absorbed in subjects with malabsorption. Nevertheless, these subjects absorbed digoxin from capsules better than from tablets, with the greatest differences occurring in subjects without a colon and in those subjects with the lowest serum carotene concentrations.

Seven subjects who underwent jejunoileal bypass surgery for massive obesity participated in a study to examine the relative bioavailability of digoxin before and one to two months after surgery[106]. They were given a loading dose of 1 mg digoxin in divided oral doses followed by oral maintenance doses of 0.5 mg daily. There were no significant differences in the area under the serum concentration time curve, steady state serum levels or 24 hour steady state excretion of digoxin before and after surgery. It was concluded that the bioavailability of digoxin from the Lanoxin tablets employed is not impaired in these patients.

Cancer Chemotherapy: The acute and chronic side effects of cancer chemotherapy on the intestinal absorption of digoxin in adult patients with neoplastic diseases was investigated[107]. The serum digoxin level fell in 7 of 8 patients by 43% at the first day (p less than 0.01) and normalized after one week. Electron microscopy of the jejunal biopsy specimens revealed damages of the microvilli and defects in the glycocalix. Acute and chronic malabsorption after cancer chemotherapy should be considered in patients, who are treated with enteral medication and nutrition.

Drug Interactions

Given the narrow therapeutic index of digoxin, it is important to understand the impact of drug interactions. The reviewer performed simulations, the percentages of patients with steady state concentrations greater than 2 ng/mL were calculated and are shown below. The target serum digoxin concentration (SDC) was 1 ng/mL.



E. General Biopharmaceutics

Formulation Details

1. What is the composition of the elixir formulation?

The composition of the elixir formulation is as follows:

Item Number	Component	Formula	Placebo
6089400	Digoxin, USP	0.05 mg	
6119000	Glycerin, USP		
6275600	Sorbitol Solution		
6266000	Sodium Citrate, USP		
6174000	Methylparaben, NF	0.1% w/v	
6241000	Propylparaben, NF	0.02% w/v	
6015000	Alcohol, USP (190 Proof) (plus 5% excess)	10.0% v/v	10.5% v/v*
6153200	Lime, imitation		
	Water	qs	qs

* 10.5% v/v ethanol, 110.5 mL Alcohol, USP (190 Proof) per L

Bioequivalence

1. Is the Roxane elixir formulation bioequivalent to Lanoxin® tablets?

Yes. The Roxane elixir formulation is bioequivalent to the Lanoxin® tablets in fasted and fed condition.

2. Is the Roxane elixir formulation bioequivalent to Lanoxin® elixir?

No. The Roxane elixir formulation is not bioequivalent to Lanoxin® elixir. Therefore Lanoxin® elixir and the Roxane elixir should not be substituted.

Food-Effect

1. What are the changes in rate and extent of absorption of digoxin when the elixir formulation is taken after meals?

When the elixir is taken after meals, the peak serum concentrations increase by 20% and the total amount of digoxin absorbed increase by 43%. The rate of digoxin absorption is unchanged.

D. Analytical Section

1. How was digoxin measured in the bioequivalence studies?

Digoxin was quantitated at [redacted] using [redacted] LC/MS analysis using [redacted] The standard curve calibration range was from 0.05-2 ng/mL in plasma. The inter-day precision for digoxin ranged from 13.5% (0.15 ng/mL) to 18.1% (1.50 ng/mL), with accuracy ranging from 98.8% (1.50 ng/mL) to 111% (0.150 ng/mL). The intra-day precision for digoxin ranged from 12.3% (1.50 ng/mL) to 17.3 (0.750 ng/mL) with accuracy ranging from 107% (0.150 ng/mL) to 115% (1.50 ng/mL). The LLOQ was found to be 0.05 ng/mL. The percent recoveries for digoxin ranged from [redacted] The recovery of the internal standard (digitoxin) was found to be 53%. The bench top (24 h) and freeze-thaw stability (3 cycles) are in the acceptable limits.

2. What is the impact of non-specific assay method used in various studies reported in literature?

Often in the literature it has been stated that the lack of clear relationship between digoxin serum concentrations and efficacy/safety is the nonspecificity of the assay method. Digoxin is routinely measured in serum by immunoassay.

The cross reactivity of the metabolites of digoxin with the antidigoxin antibodies is well known. Measurement of digoxin concentrations in serum with nonspecific antibodies 6 to 24 h after a dose clearly can lead to problems with interpretation. This is probably the reason for the lack of a consensus as to the correlation of serum digoxin concentration with either its therapeutic or toxic effects. Some investigators have found a good relationship between serum digoxin concentration and indices of improved contractility[108-110]; others have not[111-114]. Serum contains several digoxin-like immunoreactive substances (DLIS) that cross react with antidigoxin antibodies. Although the concentration of DLIS in sera from normal individuals is usually below the detection limit of a digoxin immunoassay, the concentrations of DLIS can be significantly higher elevated in certain volume expanded states such as liver failure, renal disease, essential hypertension, new born infants and premature babies[115]. The presence of EDLS (Endogenous Digoxin Like Substances) was shown to contribute to excessive levels of digoxin in children[116]. Studies have shown that excessive serum concentration levels of digoxin may not necessarily reflect potentially toxic levels[117, 118]. Elevated DLIS concentrations are encountered in patients with volume-expanded conditions such as uremia, essential hypertension, liver disease, and preeclampsia[119]. DLISs cross-react with antidigoxin antibodies and falsely elevate serum digoxin concentrations, interfering in interpretation of results for therapeutic digoxin monitoring. Falsely lower digoxin values due to the presence of DLISs have been reported. The association of DLISs with volume expansion led to speculation that they could be natriuretic hormones. Several structures have been proposed for DLISs, including nonesterified fatty acid, phospholipid, lysophospholipid, bile acid, bile salt, and steroid. Exogenous DLISs can be found in serum after ingestion of various Chinese medicines and therapy with spironolactone, canrenone, or potassium canrenoate. Like endogenous DLISs, exogenous DLISs interfere with serum digoxin assays, complicating therapeutic digoxin monitoring. However, most reported endogenous and exogenous DLISs are strongly protein-bound while digoxin is weakly protein-bound. Therefore, interference of both

endogenous and exogenous DLISs in serum digoxin measurement can be eliminated by monitoring digoxin concentrations in the protein-free ultrafiltrates.

Detailed Labeling Recommendations

The label of digoxin elixir has been updated to reflect the latest understanding of the various drug-digoxin interactions and their mechanisms. The update was mostly based on approved language from Electronic Physician's Desk Reference and also based on literature collected by the reviewer. Other minor changes are also mentioned in the label accordingly.

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34 Page(s) Withheld

_____ Trade Secret / Confidential

__✓__ Draft Labeling

_____ Deliberative Process

B. Individual Study Review

Bioequivalence Studies

DIGO-01: Bioequivalence of Roxane's digoxin elixir, 0.05 mg/ml and Glaxo Wellcome's Lanoxin tablet, 0.25 mg under fasted conditions.

DIGO-02: Bioequivalence of Roxane's digoxin elixir, 0.05 mg/ml and Glaxo Wellcome's Lanoxin tablet, 0.25 mg under fed conditions.

DIGO-03: A pilot study to assess the comparative bioavailability of Roxane Laboratories digoxin elixir, 0.05 mg/ml and GlaxoSmithKline's Lanoxin Elixir, 0.05 mg/ml, and Lanoxin Tablet, 0.25 mg, using a single-dose, randomized, 3-treatment, 3-period, 6-sequence crossover design.

Study	:	DIGO-01
Title	:	A Single Dose, Two-Way Crossover Bioequivalence Study of Digoxin Elixir and Tablet under Fasted Conditions.
Study Investigator	:	
Study Site	:	

Objectives : The objective of the study was to assess the bioequivalence of Roxane's digoxin elixir, 0.05 mg/ml, and Glaxo Wellcome's Lanoxin Tablet, 0.25 mg, under fasted conditions using a single dose, randomized, 2-treatment, 2-period, 2-sequence crossover design.

Subjects : Twenty eight healthy adults (20-45 years)

Treatments : Test: Digoxin Elixir, 0.05 mg/ml, Lot No. 256789S
Manufacturer: Roxane Laboratories, Inc.
Reference: Lanoxin Tablets, 0.25 mg, Lot No. 1ZP2396
Manufacturer: GlaxoSmithKline

Subjects received a single oral 1 mg dose if digoxin on two occasions (Periods 1 and 2). The test and reference formulations were administered according to a randomization schedule. Both doses were administered with 240 ml water after an overnight fast.

Subjects received a single oral dose on Day 1 Treatment Period 1, subjects remained in the study unit for 48 hours and then returned for the 72 and 96 hour blood samples. After a 14 day washout period, the same subjects returned for Treatment Period 2. Each subject received a single 1 mg dose in each of the two treatment periods.

Pharmacokinetic Measurements and Analytical Methods

Blood samples (10ml) were collected at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72 and 96 hours after each dose. Plasma samples were analyzed using an LC/MS method at [redacted]

The standard calibration range for digoxin is from 0.05 ng to 2 ng per ml plasma. The accuracy was 91.6, 96.5 and 98.9% for low (0.150 ng/ml), medium (0.750 ng/ml) and high (1.50 ng/ml) quality control samples respectively. The corresponding values for precision were 19.1, 16.4 and 16.7% for low (0.150 ng/ml), medium (0.750 ng/ml) and high (1.50 ng/ml) respectively.

Phamacokinetic and Statistical Methods

Maximum plasma concentrations (C_{max}), time to C_{max} (t_{max}) and area under the plasma concentration time from zero to the last time wuth a concentration $\geq$ LOQ (AUC_{0-t}) and to infinity ($AUC_{0-\infty}$) were estimated using noncompartmental analysis. Mean values for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were compared using an analysis of variance (ANOVA) statistical model with calculation of 90% confidence intervals for the ratio of test formulation to reference formulation. Bioequivalence was concluded if the 90% confidence intervals were within the 80%-125% window.

Results

The mean plasma digoxin concentrations for the Roxane Elixir and the Lanoxin tablet are shown in Figure 1. The mean values for Cmax, AUC0-t and AUC0-∞ are shown in Table 1. The 90% confidence intervals are shown in Table 2.

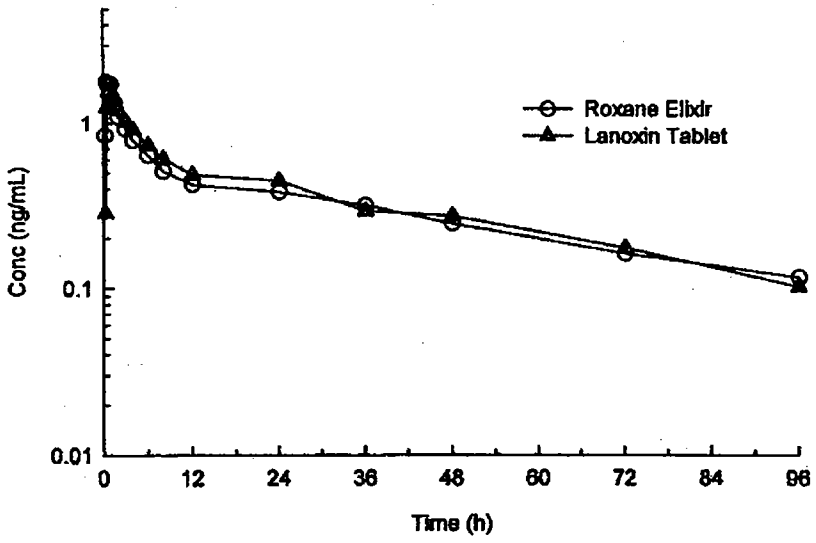

Figure 1. Mean plasma concentrations of digoxin after oral administration of single 1 mg doses of Roxane Laboratories Digoxin Elixir and Lanoxin Tablets to healthy volunteers under fasted conditions.

Table1: Digoxin pharmacokinetic parameters after oral administration of single 1 mg doses of Roxane Laboratories Digoxin Elixir and Lanoxin Tablets to healthy volunteers under fasted condition.

Parameter[1]	Roxane Digoxin Elixir	Lanoxin Tablet
Cmax (ng/mL)	2.08 ± 0.63	1.93 ± 0.64
Tmax (h)	0.75	1.00
$AUC_{0\rightarrow t}$ (h•ng/mL)	29.4 ± 10.1	31.8 ± 9.36
AUC_{∞} (h•ng/mL)	34.9 ± 14.0	37.5 ± 9.53
t½ (h)	32.3 ± 6.90	32.4 ± 6.54

[1]Arithmetic ean ± standard deviation except for Tmax for which the median is reported.

Table 2: Statistical Comparison of digoxin pharmacokinetic parameters after oral administration of single 1mg doses of Roxane Laboratories Digoxin Elixir and Lanoxin Tablets to healthy volunteers under fasted conditions.

Parameter	Ratio (%)[1]	
	Point Estimate	90% Confidence Interval
Cmax	107.9	95.8 → 121.5
AUC_{0-t}	90.2	83.6 → 97.3
AUC_{∞}	95.0	87.5 → 103.2

[1]Geometric matio of the Test to the Reference. Based on analysis of natural log-transformed data.

Conclusion

The 90% confidence intervals for the ratio, test-to-reference for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were within 80-125% window indicating that the Roxane Laboratories Elixir is bioequivalent to Lanoxin tablets under fasted conditons.

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Study	:	DIGO-02
Title	:	A Single Dose, Two-Way Crossover Bioequivalence Study of Digoxin Elixir and Tablet under Fed Conditions.
Study Investigator	:	
Study Site	:	

Objectives : The objective of the study was to assess the bioequivalence of Roxane's digoxin elixir, 0.05 mg/ml, and Glaxo Wellcome's Lanoxin Tablet, 0.25 mg, under fed conditions using a single dose, randomized, 2-treatment, 2-period, 2-sequence crossover design.

Subjects : Twenty six healthy adults (18-45 years)

Treatments : Test: Digoxin Elixir, 0.05 mg/ml, Lot No. 256789S
Manufacturer: Roxane Laboratories, Inc.
Reference: Lanoxin Tablets, 0.25 mg, Lot No. 1ZP2396
Manufacturer: GlaxoSmithKline

Subjects received a single oral 1 mg dose if digoxin on two occasions (Periods 1 and 2). The test and reference formulations were administered according to a randomization schedule. Both doses were administered with 240 ml water after a standard meal preceded by an overnight fast.

Subjects received a single oral dose on Day 1 Treatment Period 1, subjects remained in the study unit for 48 hours and then returned for the 72 and 96 hour blood samples. After a 14 day washout period, the same subjects returned for Treatment Period 2. Each subject received a single 1 mg dose in each of the two treatment periods.

Pharmacokinetic Measurements and Analytical Methods

Blood samples (10ml) were collected at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72 and 96 hours after each dose. Plasma samples were analyzed using an LC/MS method at

The standard calibration range for digoxin was from 0.05 ng to 2 ng per ml plasma. The accuracy was 93.8, 106 and 101% for low (0.150 ng/ml), medium (0.750 ng/ml) and high (1.50 ng/ml) quality control samples respectively. The corresponding values for precision were 19.2, 14.5 and 12.2% for low (0.150 ng/ml), medium (0.750 ng/ml) and high (1.50 ng/ml) respectively.

Phamacokinetic and Statistical Methods

Maximum plasma concentrations (C_{max}), time to C_{max} (t_{max}) and area under the plasma concentration time from zero to the last time wuth a concentration ≥ LOQ (AUC_{0-t}) and to infinity ($AUC_{0-\infty}$) were estimated using noncompartmental analysis. Mean values for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were compared using an analysis of variance (ANOVA) statistical model with calculation of 90% confidence intervals for the ratio of test formulation to reference formulation. Bioequivalence was concluded if the 90% confidence intervals were within the 80%-125% window.

Results: The mean plasma digoxin concentrations for the Roxane Elixir and the Lanoxin tablet are shown in Figure 1. The mean values for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ are shown in Table 1. The 90% confidence intervals are shown in Table 2.

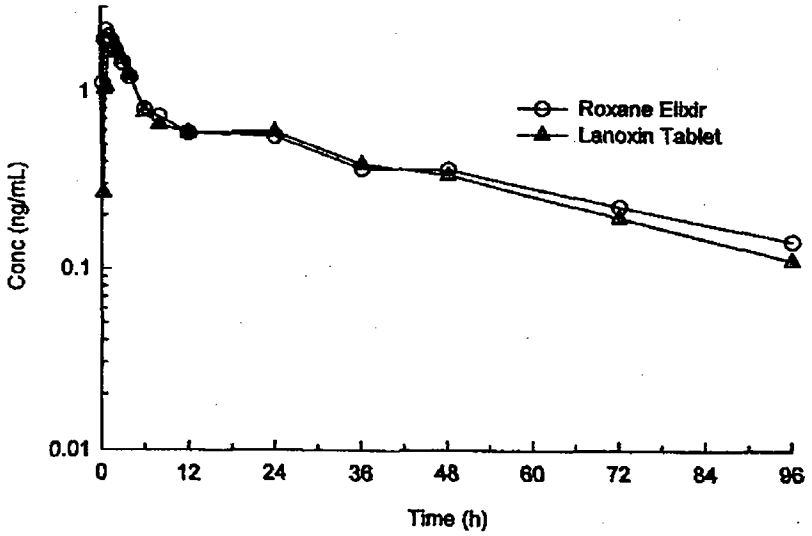

Figure 1. Mean plasma concentrations of digoxin after oral administration of single 1 mg doses of Roxane Laboratories Digoxin Elixir and Lanoxin Tablets to healthy volunteers under fed conditions.

Table1: Digoxin pharmacokinetic parameters after oral administration of single 1 mg doses of Roxane Laboratories Digoxin Elixir and Lanoxin Tablets to healthy volunteers under fed condition.

Parameter[1]	Roxane Digoxin Elixir	Lanoxin Tablet
Cmax (ng/mL)	2.53 ± 0.68	2.47 ± 0.95
Tmax (h)	1.00	1.75
AUC_{0-t} (h•ng/mL)	40.7 ± 13.2	39.0 ± 11.9
AUC_{∞} (h•ng/mL)	45.5 ± 13.7	47.0 ± 15.0
$t_{1/2}$ (h)	31.0 ± 6.67	29.4 ± 7.93

[1]Arithmetic mean ± standard deviation except for Tmax for which the median is reported.

Table 2: Statistical Comparison of digoxin pharmacokinetic parameters after oral administration of single 1mg doses of Roxane Laboratories Digoxin Elixir and Lanoxin Tablets to healthy volunteers under fed conditions.

	Ratio (%)[1]	
Parameter	Point Estimate	90% Confidence Interval
Cmax	105.2	91.8 → 120.7
AUC_{0-t}	103.4	92.1 → 116.1
AUC_{∞}	102.1	79.6 → 130.9

[1]Geometric mean ratio of the Test to the Reference. Based on analysis of natural log-transformed data.

Conclusion: The 90% confidence intervals for the ratio, test-to-reference for Cmax, AUC0-t were within 80-125% window. Although the geometric mean ratio for AUC0-∞ was 102.1%, the limits of confidence intervals were outside 80%-125%. This indicates that the Roxane Laboratories Elixir is bioequivalent to Lanoxin tablets under fed conditions with respect to C_{max}, AUC_{0-t}.

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Study	:	DIGO-03
Title	:	A Single Dose, Three-Way Crossover Comparative Bioavailability Study of Digoxin Elixirs and Tablet.
Study Investigator	:	
Study Site	:	

Objectives : The objective of the study was to assess the comparative bioavailability of Roxane Laboratories' digoxin elixir, 0.05 mg/ml, and GlaxoSmithKline's Lanoxin Elixir, 0.05 mg/ml, and Lanoxin Tablet, 0.25 mg, using a single dose, randomized, 3-treatment, 3-period, 6-sequence crossover design.

Subjects : Eighteen healthy adults (20-44 years)

Treatments : Test: Digoxin Elixir, 0.05 mg/ml, Lot No. 156280A
Manufacturer: Roxane Laboratories, Inc.
Reference A: Lanoxin Elixir Pediatric, 0.05 mg/ml, Lot No. 1D701
Manufacturer: GlaxoSmithKline
Reference B: Lanoxin Tablets, 0.25 mg, Lot No. 011184A
Manufacturer: GlaxoSmithKline

Subjects received a single oral dose of digoxin on three occasions (Period 1 through Period 3). The test and reference formulations were administered according to randomization code. All doses were administered after an overnight fast.

Subjects received a single oral dose on Day 1 Treatment Period 1, subjects remained in the study unit for 48 hours and then returned for the 72 and 96 hour blood samples. After a 14 day washout period, the same subjects returned for

Treatment Period 2 and similarly for Treatment Period 3. Each subject received a single 1 mg dose in each of the three treatment periods.

Pharmacokinetic Measurements and Analytical Methods

Blood samples (10ml) were collected at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72 and 96 hours after each dose. Plasma samples were analyzed using an LC/MS method at

The standard calibration range for digoxin was from 0.05 ng to 2 ng per ml plasma. The accuracy was 113, 104 and 101% for low (0.150 ng/ml), medium (0.750 ng/ml) and high (1.50 ng/ml) quality control samples respectively. The corresponding values for precision were 14.1, 13.9 and 12.7% for low (0.150 ng/ml), medium (0.750 ng/ml) and high (1.50 ng/ml) respectively.

Phamacokinetic and Statistical Methods

Maximum plasma concentrations (C_{max}), time to C_{max} (t_{max}) and area under the plasma concentration time from zero to the last time with a concentration ≥ LOQ (AUC_{0-t}) and to infinity ($AUC_{0-\infty}$) were estimated using noncompartmental analysis. Mean values for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were compared using an analysis of variance (ANOVA) statistical model with calculation of 90% confidence intervals for the treatment ratios (RLI Elixir:GSK Elixir; RLI Elixir:GSK Tablet; GSK Elixir: GSK Tablet). Bioequivalence was concluded if the 90% confidence intervals were within the 80%-125% window.

Results: The mean plasma digoxin concentrations for the Roxane Elixir, Lanoxin Elixir and the Lanoxin tablet are shown in Figure 1. The mean values for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ are shown in Table 1. The 90% confidence intervals are shown in Table 2.

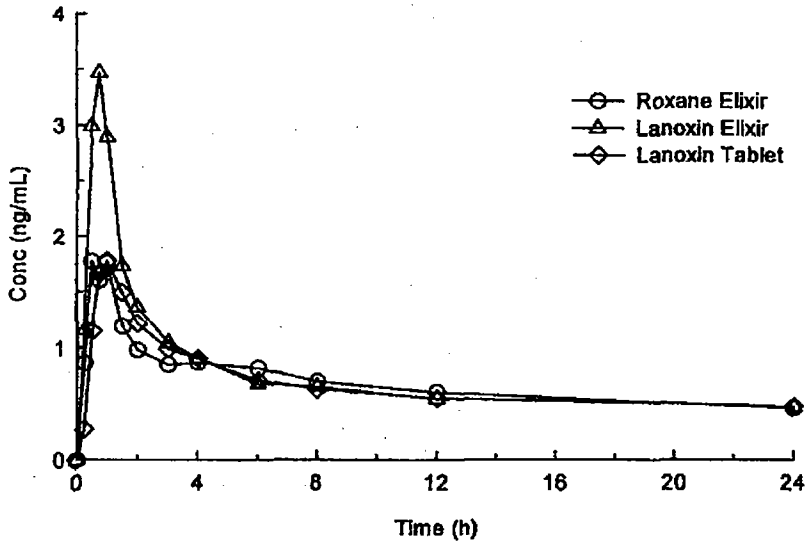

Figure 1. Mean plasma concentrations of digoxin after oral administration of single 1 mg doses of Roxane Laboratories Digoxin Elixir, Lanoxin Elixir and Lanoxin Tablets to healthy volunteers under fasted conditions (Initial 24h).

Table1: Digoxin pharmacokinetic parameters after oral administration of single 1 mg doses of Roxane Laboratories Digoxin Elixir, Lanoxin Elixir and Lanoxin Tablets to healthy volunteers under fasted conditions.

Parameter[1]	Roxane Elixir[2]	Lanoxin Elixir[3]	Lanoxin Tablet[3]
Cmax (ng/mL)	1.98 ± 0.49	3.65 ± 0.94	1.96 ± 0.43
Tmax (h)	0.750	0.750	1.000
AUC_{0-t} (h•ng/mL)	31.2 ± 8.97	34.3 ± 9.71	32.7 ± 10.7
AUC_{∞} (h•ng/mL)	36.3 ± 9.74	41.0 ± 11.3	38.3 ± 11.7
t½ (h)	32.8 ± 13.7	36.3 ± 7.33	32.1 ± 10.5

[1]Mean ± standard deviation except for Tmax for which the median is reported.
[2]N = 13
[3]N = 14

Table 2: Statistical Comparison of digoxin pharmacokinetic parameters after oral administration of single 1mg doses of Roxane Laboratories Digoxin Elixir, Lanoxin Elixir and Lanoxin Tablets to healthy volunteers under fasted conditions.

Parameter	Ratio (%)[1]	
	Point Estimate	90% Confidence Interval
Roxane Elixir vs Lanoxin Tablet		
Cmax	103.3	86.3 → 123.6
AUC_{0-t}	99.1	87.7 → 112.0
AUC_{∞}	97.3	84.6 → 112.0
Lanoxin Elixir vs LanoxinTablet		
Cmax	180.7	151.8 → 215.0
AUC_{0-t}	107.2	95.2 → 120.7
AUC_{∞}	109.6	95.7 → 125.5
Roxane Elixir vs Lanoxin Elixir		
Cmax	57.2	47.8 → 68.4
AUC_{0-t}	92.5	81.9 → 104.5
AUC∞	88.8	77.3 → 102.1

[1]Ratio of the Test to the Reference. Based on analysis of natural log-transformed data.

Conclusion: The results of the study showed that the Roxane Laboratories Digoxin Elixir was bioequivalent to Lanoxin Tablet with respect to C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. The Lanoxin Elixir was not bioequivalent to Roxane Elixir or Lanoxin tablets with respect to C_{max}.

Bioequivalence Data Re-analysis

The sponsor submitted the original serum concentration data of digoxin based on the recommendations by Division of Scientific Investigations. The sponsor also submitted the SAS code used for the bioequivalence analysis. The following are the results of the analysis performed by the reviewer:

Study DIGO-01

Table1: Digoxin pharmacokinetic parameters after oral administration of single 1 mg doses of Roxane Laboratories Digoxin Elixir and Lanoxin Tablets to healthy volunteers under fasted condition.

Parameter	*Roxane Digoxin Elixir*	*Lanoxin Tablets*
Cmax (ng/mL)	2.09 ± 0.64	1.93 ± 0.64
Tmax(h)	0.77 ± 0.27	1.21 ± 1.11
AUC0-t(ng.h/mL)	29.44 ± 12.23	30.26 ± 10.16
AUC0-∞(ng.h/mL)	35.48 ± 13.70	38.98 ± 11.17
T1/2(h)	38.73 ± 15.43	36.80 ± 9.83

Table 2: Statistical Comparison of digoxin pharmacokinetic parameters after oral administration of single 1mg doses of Roxane Laboratories Digoxin Elixir and Lanoxin Tablets to healthy volunteers under fasted conditions.

	Ratio(%)	
Parameter	Point Estimate	90% Confidence Interval
Cmax	108.3	97.0-120.9
AUC0-t	95.1	88.7-101.0
AUC0-∞	98.0	89.6-105.1

Study DIGO-02

Table1: Digoxin pharmacokinetic parameters after oral administration of single 1 mg doses of Roxane Laboratories Digoxin Elixir and Lanoxin Tablets to healthy volunteers under fed condition.

Parameter	*Roxane Digoxin Elixir*	*Lanoxin Tablets*
Cmax (ng/mL)	2.53 ± 0.68	2.47 ± 0.95
Tmax(h)	1.15 ± 0.69	1.71 ± 0.89
AUC0-t(ng.h/mL)	39.97 ± 12.47	39.13 ± 12.15
AUC0-∞(ng.h/mL)	50.82 ± 20.15	46.87 ± 13.62
T1/2(h)	38.90 ± 18.68	34.03 ± 10.43

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Table 2: Statistical Comparison of digoxin pharmacokinetic parameters after oral administration of single 1mg doses of Roxane Laboratories Digoxin Elixir and Lanoxin Tablets to healthy volunteers under fed conditions.

	Ratio(%)	
Parameter	Point Estimate	90% Confidence Interval
Cmax	104.1	92.3-119.7
AUC0-t	104.1	94.2-116.2
AUC0-∞	107.3	94.2-122.1

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Study DIGO-03

Table1: Digoxin pharmacokinetic parameters after oral administration of single 1 mg doses of Roxane Laboratories Digoxin Elixir and Lanoxin Tablets to healthy volunteers under fasted condition.

Parameter	*Roxane Digoxin Elixir*	*Lanoxin Elixir*	*Lanoxin Tablets*
Cmax (ng/mL)	1.97 ± 0.48	3.64 ± 0.93	1.96 ± 0.42
Tmax(h)	0.71 ± 0.22	0.75 ± 0.15	1.00 ± 0.37
AUC0-t(ng.h/mL)	31.19 ± 8.96	34.11 ± 9.57	32.97 ± 10.65
AUC0-∞(ng.h/mL)	36.26 ± 9.73	41.30 ± 11.34	38.59 ± 12.12
T1/2(h)	32.75 ± 13.67	36.44 ± 7.58	31.90 ± 10.86

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Table 2: Statistical Comparison of digoxin pharmacokinetic parameters after oral administration of single 1mg doses of Roxane Laboratories Digoxin Elixir and Lanoxin Tablets to healthy volunteers under fasted conditions.

	Ratio(%)	
Parameter	Point Estimate	90% Confidence Interval
Roxane Elixir vs Lanoxin Tablet		
Cmax	103.0	86.9-123.4
AUC0-t	99.0	87.8-110.5
AUC0-∞	98.0	84.4-112.7
Lanoxin Elixir vs Lanoxin Tablet		
Cmax	180.4	150.7-213.8
AUC0-t	105.1	94.2-118.5
AUC0-∞	110.5	96.1-127.1
Roxane Elixir vs Lanoxin Elixir		
Cmax	57.7	48.2-68.4
AUC0-t	93.2	82.7-104.1
AUC0-∞	88.7	76.3-101.0

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C. Summary of Pharmacokinetic Studies in literature

To address this question, first a summary of the pharmacokinetic studies in literature are discussed. Comments by the reviewer are also mentioned for each study followed by an overall discussion and conclusion.

Title: Serum digoxin levels in neonates whose weights are less than 1500 grams.

Author: Patterson et al.

In this study digoxin was administered to 29 infants in congestive heart failure and weighing less than 1500 grams[46]. The initial digitalizing dose varied widely over the range of 20-60 µg/kg. In nearly all patients digoxin was administered by intravenous injection and the initial dose divided over 24 hours with maintenance therapy continued at 20-30% of the dose. Half of the daily dose was given parenterally every 12 hours. Serum digoxin was measured after at least 4 days of maintenance therapy. Blood was taken between 6 and 12 hours after the last dose of digoxin. The serum digoxin concentrations were measured by radioimmunoassay. The relationship between serum digoxin concentrations and dose is shown in figure below.

Analytical Method:

Radioimmunoassay

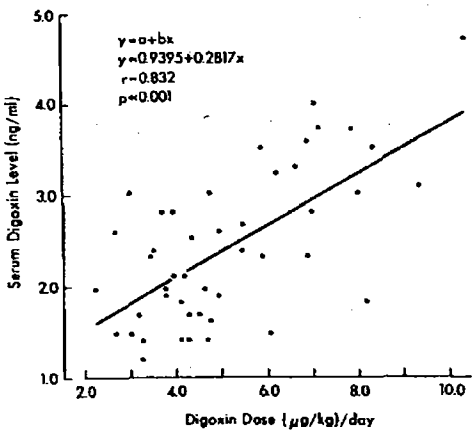


Fig. 1 Relationship of daily digoxin dose to serum digoxin level in 29 premature infants under 1,500 gm.

The study published as shown above was performed using radioimmunoassay which was developed in 1969. In later years that followed the publication of this study, it was discovered that EDLS can cause false elevation of digoxin concentrations. Since this issue was not addressed at the time of the study, the results are not reliable to use for dosing recommendations.

Maintenance digoxin dosage and steady-state plasma concentration in infants and children[47].

A prospective study of digoxin plasma concentrations in 644 children of different ages and weights from 1979-1983 was conducted[47]. Achievement of steady state concentrations was presumed on the following grounds:

1. All children were receiving a constant digoxin maintenance dose of digoxin for at least 5 days.
2. Blood samples were drawn at 6 to 12 hours after digoxin dosing.

Subjects receiving the drug orally were divided into three groups

Group	Age	Dose (µg/kg/day)
1	Infants < 3months of age weighing < 1500 gm.	5
2	Infants < 3 months of age weighing 1500 to 2500 gm.	7.5
3	Infants < 3 months, weighing > 2500 gm.	10
4	3 to 6 months.	10
5	7 to 12 months.	10
6	13 to 24 months.	10
7	2 to 5 years.	10
8	6 to 10 years.	5
9	11 to 20 years.	5

Analytical Method:

Plasma digoxin was measured by three different radioimmunoassay kits.

1. 125I-digoxin immunoassay, Abbott Laboratories, North Chicago, Ill.
2. Spac, Malinckdrot Inc.,
3. Quantitope, Kallestad Laboratories Inc., Austin Texas.

The relationship between serum digoxin concentrations and digoxin dose is shown below.

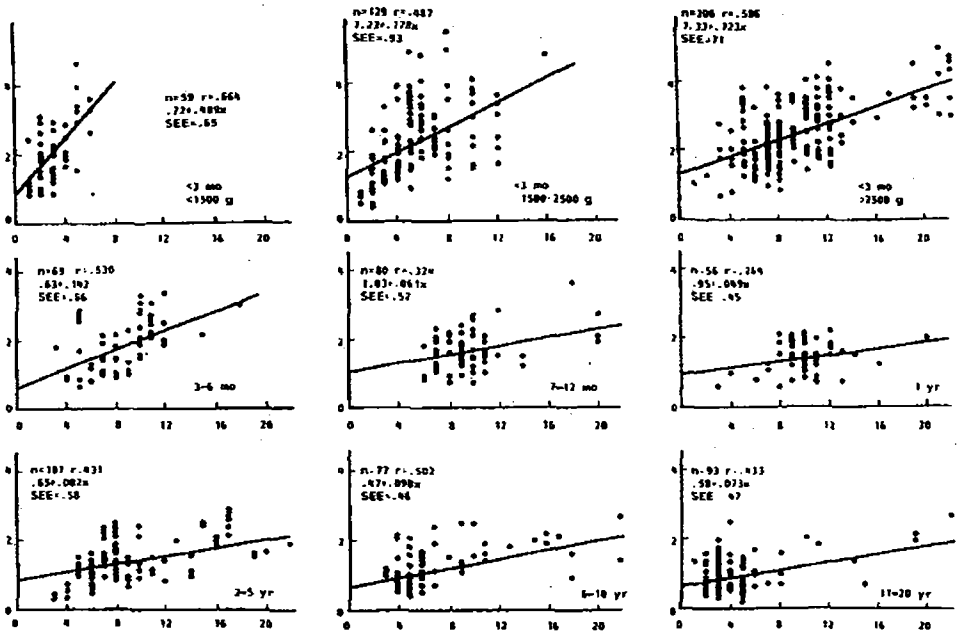


Fig. 2. Plots of digoxin plasma concentration (in ng/ml; *ordinate*) vs dosage (in μg/kg/day; *abscissa*) for each age and weight group of infants and children who received digoxin orally. Correlation coefficient (r), intercept, and slope of linear regression equation, and standard error of estimate (*SEE*) are shown. Regression lines are drawn to illustrate changes in slopes with age.

Reviewer Comments:

1. The linear regression model as shown above is not reliable due to the high positive intercept on Y-axis. The intercept is ~1 ng/mL which is equivalent to the therapeutic concentrations.

   According to the authors "At the end of the study in 1983, several reports appeared indicating the presence of EDLS in serum of neonates who did not receive therapy with digoxin". The authors state that "A significant error in digoxin measurement in our neonatal population (Groups 1 to 3) may have been caused by EDLS. Our own analysis suggested that the error was small, but was not totally conclusive that the error was small because it involved only one of the three RIA kits we used." In light of these facts, the data from this study cannot be used for dosage calculations for age groups less than 3 months of age.

2. The investigators used 3 different RIA kits for digoxin analysis. The authors evaluated the cross-reactivity with EDLS only for Quantitope kit as it was used for 40% of the analyses. The authors did not evaluate the crossreactivity of the other kits. This aspect adds an extra concern to the overall data.

Serum digoxin levels in neonates, infants and children with heart disease[120].

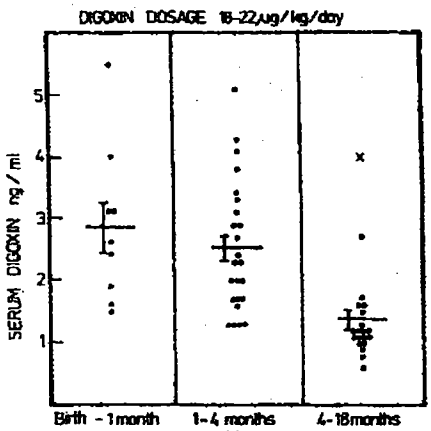
Studies were carrried out in neonates, infants and children with heart failure. Eighty one had congenital heart disease, 10 had rheumatic heart disease and six had cardiac myopathy[120]. No prematurely born infants were included in this study.

Group1: 53 neonates and infants with heart failure received 18-22 ug/kg/day of oral digoxin in two divided doses. 9 patients were under 1 month of age, 24 were 1-4 months and 20 were 4-18 months. All patients received Lanoxin Elixir for at least one week prior to the test date. Blood samples were drawn 7-12 hours after the last dose of digoxin.

Group2: 44 patients received less than 18 ug/kg/day of digoxin. 6 patients were under 1 month of age, 11 were 1-4 months, 12 were 4-18 months and 15 were 18 months-17 years. 11 patients in the older age group received digoxin as Lanoxin tablets.

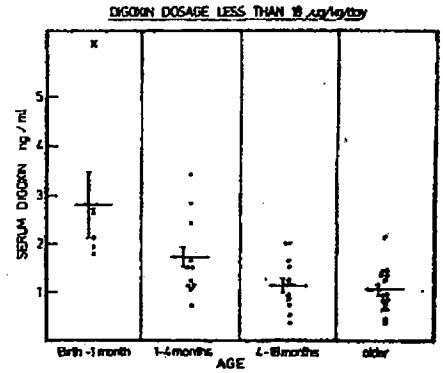
Analytical Method:

RadioimmunoassayThe serum digoxin levels of patients in both dose groups are shown below:



	Birth - 1 month	1-4 months	4-18 months
Digoxin dose µg/kg	19·7 ± 0·9	19·4 ± 1·7	19·6 ± 2·4
Digoxin dose µg/m²	318·0 ± 10·0	314·0 ± 13·0	359·0 ± 9·7
Blood urea mmol/l	4·1 ± 0·5	5·1 ± 0·5	6·9 ± 0·5

Figure 1.—Levels of serum digoxin in neonates and infants receiving 18–22 µg/kg/day oral maintenance digoxin. Means ± SEM. x = patient with clinical evidence of toxicity.



	Birth - 1 month	1-4 months	4-18 months	older
Digoxin dose µg/kg	15·9 ± 0·8	14·4 ± 0·2	14·5 ± 0·6	9·8 ± 0·7
Digoxin dose µg/m²	257·0 ± 13·0	232·0 ± 13·0	269·0 ± 9·1	244 ± 17·0
Blood urea mmol/l	4·8 ± 1·2	4·8 ± 0·5	8·9 ± 1·5	8·3 ± 1·7

Figure 2.—Levels of serum digoxin in neonates, infants and children receiving less than 18 µg/kg/day oral maintenance digoxin. x = patient with clinical evidence of toxicity.

Reviewer Comments

1. The analytical method used by the investigators is not free from EDLS. This would make the data from neonates less reliable.
2. The data from the older age groups (> 4months) might be more reliable as literature cites that greater than 2-3 months of age, the interference from EDLS decreases. A dose of 12 ug/kg/day in age groups of 4-18 months and 8 ug/kg/day in older age groups (18 months to 17 years) would be required to achieve steady state concentrations of 1 ng/mL.
3. The investigators did not find any correlation between serum digoxin levels and the degree of control of heart failure as assessed by pulse rate, respiratory rate, hepatomegaly and chest x-ray.

Results:

1. The serum concentrations were 1.7-3.4 nmol/L (1.3-2.65 ng/mL) at steady state after a maintenance dose of 7-10 ug/kg/day.

Reviewer Comments:

1. The analytical method used by the investigators was not free from interference due to EDLS. Hence the reported serum digoxin concentrations in neonates cannot be relied upon.
2. The investigators proposed maintanence doses of 15-25 ug/kg/day in infants to achieve serum concentrations of 1.56 ng/mL.

Population based investigation of relative clearance of digoxin in Japanese neonates and infants by multiple-trough screen analysis[121].

Routine clinical data (448 observations) were collected from 172 patients, among them 8 premature patients in Kyushu Kosei-Nenkin hospital between 1994-1997, who were twice administered a powder preparation of digoxin, which was diluted with water[121]. The data showing steady state after repetitive oral administration in 172 hospitalized neonates and infants were analyzed using NONMEM. The summary of the patient characteristic data is shown in table below:

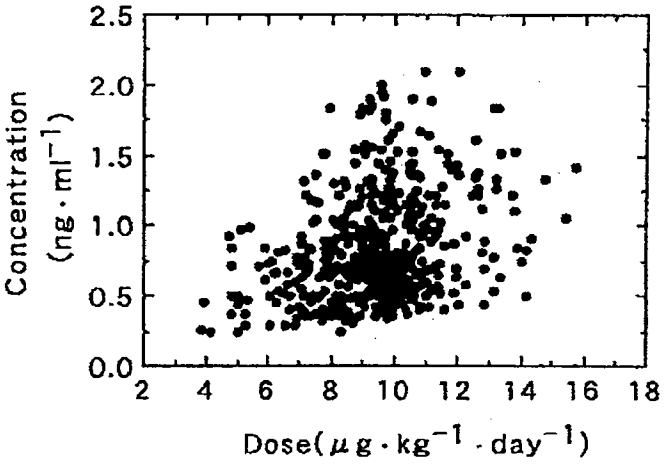
Table 1 Summary of patient data. Values in parentheses indicate males. *SPI (+)* with coadministration of spironolactone, *CHF (+)* with congestive heart failure. *Premature* birth before the 37th gestational week

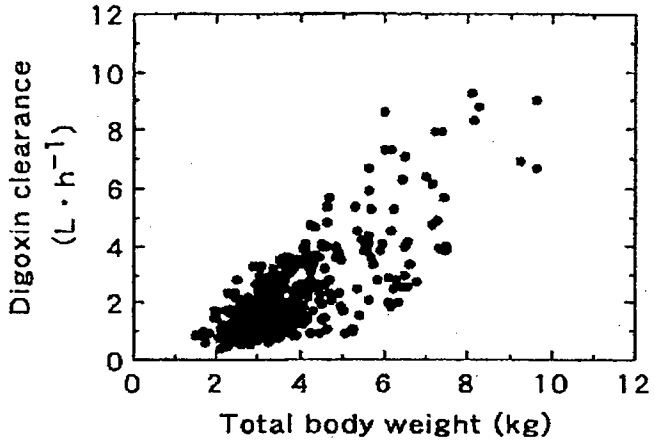
Characteristic	Modeling	Validation
Number of patients	172 (96)	66 (35)
Premature	8 (6)	0
Number of observations	448 (261)	81 (43)
SPI (+)	378 (216)	67 (32)
CHF (+)	265 (146)	62 (34)
Premature	9 (6)	0
Age (days, mean ± SD)	86.4 ± 79.0	92.1 ± 88.9
Range	8~362	12~362
Total body weight (kg, mean ± SD)	3.66 ± 1.31	3.99 ± 1.45
Range	1.49~9.65	2.10~8.21
Dose ($\mu g \cdot kg^{-1} \cdot day^{-1}$, mean ± SD)	9.40 ± 1.92	9.69 ± 1.81
Range	3.82~15.72	4.76~13.30
Steady-state concentrations ($ng \cdot ml^{-1}$, mean ± SD)	0.84 ± 0.39	0.85 ± 0.35
Range	0.24~2.10	0.29~1.83

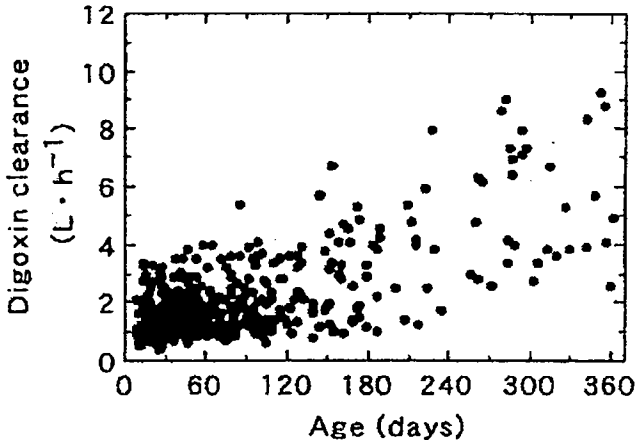
Analytical Method:

Serum digoxin concentration were carried out using COBAS-FARA (Hoffman-La Roche, Inc., Nutley, N. J). The measurements made using this method were free from EDLS.

The relationship between digoxin dose and serum concentration is shown below.


Concentration
(ng · ml^{-1})
2.5
2.0
1.5
1.0
0.5
0.0
2
4
6
8
10
12
14
16
18
Dose(μg · kg^{-1} · day^{-1})


Digoxin clearance
(L · h^{-1})
12
10
8
6
4
2
0
0
2
4
6
8
10
12
Total body weight (kg)


Digoxin clearance
(L · h^{-1})
12
10
8
6
4
2
0
0
60
120
180
240
300
360
Age (days)

Reviewer Comments:

1. The investigators used a good analytical method to determine the serum concentrations of digoxin. The analytical method, as stated by the authors, is free from interference from EDLS[122]. This makes the data and the derived pharmacokinetic parameters more reliable to accept.
2. The positive intercept seen in the concentration vs dose relationship in this study is much lower than that in study reported by Hastreiter. This would make the relationship between dose and concentration more reliable.
3. Suematsu et al used powder formulation in their study. They report that the bioavailability from powder formulation is 25.3% less than that of elixir. In the dosage calculations, proposed by the reviewer, this difference was taken in account.

Population pharmacokinetics of digoxin in pediatric patients[123].

A retrospective study was carried out in 51 pediatric patients (Age: 0.2-12 months; Body Weight: 2.3-7.2 kg)[123]. Digoxin was administered to some patients as intravenous bolus and to others as elixir. The digoxin doses ranged from 2.53-20.47 µg/kg/day. Patients receiving drugs known to interact with digoxin were excluded from the study.

Analytical Method:

Digoxin concentrations in serum samples were analyzed using an immunofluorescent polarization method (TDx Digoxin II assay, Abbott Laboratories Ltd).

The data was analyzed using NONMEM (Ver IV) and the model describing the relationship between clearance, age is shown below:

$$\mathrm{Cl(L/h/kg)} = 0.237(1 + 0.094 * \mathrm{AGE\ (months)})$$

Reviewer Comments:

The assay method used by the investigator is reliable[124]. This would make the data more reliable.

Population analysis for the optimization of digoxin treatment in Japanese pediatric patients[44].

The investigators collected serum digoxin concentrations (n=544) from 181 pediatric patients. The purpose of the analysis was to investigate the effects of dose, age and other physiological factors on digoxin serum concentration in Japanese pediatric patients. In addition, the influence of the coadministration of spironolactone and the presence or absence of congestive heart failure (CHF) on digoxin clearance was also investigated.

The details of patients included in the population pharmacokinetic analysis is shown below:

Table 1. Details of patients included in this populatation pharmacokinetics analysis

	Age group			
	A <4 month	B 4 months–3 years	C > 3 years	Total
Number of patients				181 (M 92, F 89)
CHF (+)				80 (M 41, F 39)
Number of points	311 (M 202, F 109)	186 (M 78, F 108)	47 (M 22, F 25)	544 (M 302, F 242)
CHF (+)	166 (M 97, F 69)	42 (M 17, F 25)	4 (M 1, F 3)	212 (M 115, F 97)
Age (years)	0·14 ± 0·08	1·39 ± 0·92	5·65 ± 1·49	1·05 ± 1·68
	(0·03–0·33)	(0·33–3·96)	(4·03–9·36)	(0·03–9·36)
Total body weight (kg)	3·21 ± 0·74	7·50 ± 3·36	15·52 ± 3·19	5·74 ± 4·24
	(1·43–6·35)	(1·78–15·00)	(11·20–27·20)	(1·43–27·20)
Serum creatinin (mg/dL)	0·28 ± 0·13	0·25 ± 0·07	0·29 ± 0·07	0·27 ± 0·11
	(0·1–1·1)	(0·10–0·50)	(0·20–0·40)	(0·1–1·1)
Dose (mg)	0·03 ± 0·01	0·06 ± 0·03	0·11 ± 0·02	0·05 ± 0·03
	(0·01–0·07)	(0·02–0·12)	(0·08–0·15)	(0·01–0·15)
Dose (mg/kg/d)	9·25 ± 1·93	8·71 ± 2·02	7·36 ± 1·71	8·90 ± 2·01
	(3·82–15·73)	(3·88–19·61)	(3·68–10·53)	(3·68–19·61)
C/D ratio (ng ml per μg/kg/d)	0·096 ± 0·045	0·075 ± 0·033	0·098 ± 0·028	0·089 ± 0·041
	(0·03–0·23)	(0·02–0·23)	(0·05–0·18)	(0·02–0·23)
Digoxin concentration (ng/ml)	0·88 ± 0·42	0·64 ± 0·28	0·70 ± 0·20	0·78 ± 0·38
	(0·19–2·10)	(0·21–1·99)	(0·38–1·25)	(0·19–2·10)
Digoxin clearance (L/d)	41·45 ± 22·25	111·52 ± 54·07	166·66 ± 44·85	76·23 ± 57·27
	(10·26–129·03)	(17·86–279·07)	(104·00–300·00)	(10·26–300·00)

Mean ± SD (range)

Analytical Method: Digoxin concentration measurement reagent CEDIA Digoxin II (Yamanouchi Pharmaceutical Co., Ltd, Tokyo, Japan) based on cloned enzyme donor im- munoassay (the method of CEDIA) was used, and measured by COBAS- FARA (F. Hoffmann La Roche Inc, Nutley, NJ). The coefficient of variation of this assay was less than 10%. The method is relatively free from the effects of a digoxin- like immunoreactive substance (EDLS).

The relationship between clearance vs dose is shown below:

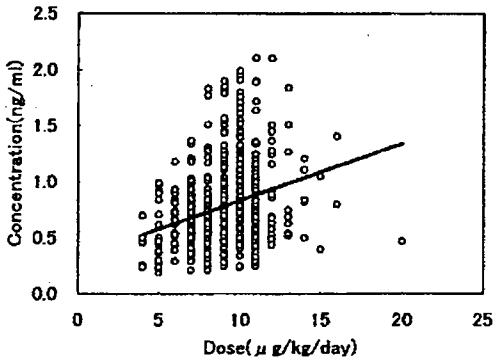


Fig. 1. Relationship between digoxin dose and serum digoxin concentration. $y = 0{\cdot}05x + 0{\cdot}33$; $r = 0{\cdot}278$.

The relationship between clearance, age and body weight are shown below:

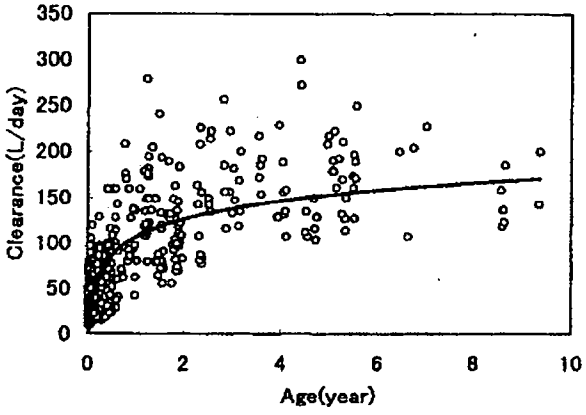


Fig. 2. Relationship between digoxin clearance and age. $y = 28{\cdot}71$ Ln $(x) + 106{\cdot}84$; $r = 0{\cdot}766$.

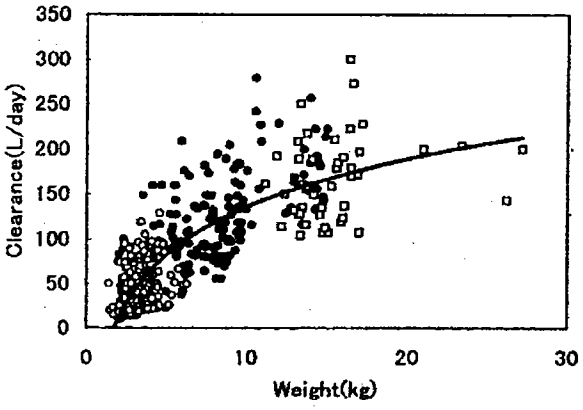


Fig. 3. Relationship between digoxin clearance and total body weight. $y = 77{\cdot}58$ Ln $(x) - 43{\cdot}06$; $r = 0{\cdot}810$. (○ = group A; ● = group B; □ = group C)

The digoxin clearance in various age groups are shown below:

	n	CL (L/d) (mean ± SD)
<1 month	93	36·3 ± 20·6
1–2 months	109	41·2 ± 20·8
2–3 months	63	46·2 ± 24·2
3–4 months	46	45·8 ± 23·7
4–5 months	19	59·3 ± 34·0
5–6 months	22	66·7 ± 40·0
6–12 months	37	94·3 ± 43·7
1–2 years	72	123·3 ± 43·7
2–3 years	22	155·6 ± 51·3
3–4 years	14	168·6 ± 33·1
4–5 years	17	160·6 ± 56·7
5–6 years	19	173·6 ± 33·6
6–7 years	3	170·5 ± 44·6
> 7 years	8	161·7 ± 36·4

* ng/ml per μg/kg/d

Reviewer Comments:

1. The investigators used a good analytical method to determine the serum concentrations of digoxin. The analytical method, as stated by the authors, is free from interference from EDLS. This makes the data and the derived pharmacokinetic parameters more reliable to accept.
2. Suematsu et al used powder formulation in their study. They report that the bioavailability from powder formulation is 25.3% less than that of elixir. In the dosage calculations, proposed by the reviewer, this difference was taken in account.

Discussion

1. The linear relationship between serum concentrations and dosage in various age groups as proposed by Hastreiter is biased. This is because of the intercept on the Y-axis being greater than 1 ng/mL. The high positive intercept is due to the (A) Assumption of linear relationship (B) Three different RIA kits used in the analysis of serum digoxin concentrations. These findings would make the regression equation showing the relationship between digoxin concentrations and dose unreliable to use for dosage recommendations.

2. Hastreiter et al in Table I provide the estimates of clearance after oral administration. The reviewer used these values to calculate dosing recommendations.

3. Suematsu et al used powder formulation in their study. They report that the bioavailability from powder formulation is 25.3% less than that of elixir. In the dosage calculations, proposed by the reviewer, this difference was taken in account.

4. Dosing recommendations for age groups less than 1 year calculated based on Suematsu et al and Suarez et al are in good agreement for some age groups . These are however, quite different from Hastreiter etal.

5. The dosage recommendations for pediatric population to target 1.5 ng/mL based on published information by Suematsu, Hafstreiter, Patterson and Suarez are shown in table below.

Comparison of dosing recommendations by Suematsu, Suarez, Hafstreiter and Patterson. The labeling recommendations for age groups in LANOXIN tablets label is also shown here.

Age	*Suematsu*	*Suarez*	*Hastreiter Equation based*	*Hastreiter CL based*	*Patterson*	*LANOXIN tablets*
< 3months	15-16	12-14	1-2	2-5	3	-
3-6months	16-18	14-17	6	6	-	-
7-12months	18	18-22	8	8	-	-
1year	16	23	11	9	-	-
2-5year	12-14	-	10	8	-	10-15
6-10year	12	-	11	6	-	7-10
11-20 years	-	-	13	5	-	3-5

Note: The dosing recommendations were calculated to achieve a steady state concentration of 1.5 ng/mL. The dosing recommendations by Nyberg (10-16 ug/kg/day in infants) and Neutze (18 ug/kg/day in 4-18 months; 12 ug/kg/day in 18 months-17 years) et al are also similar to those calculated based on Suematsu data.

D. Filing and Review Form

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		Information
NDA Number	21-648	Brand Name	Digoxin Elixir USP
OCPB Division (I, II, III)	DPE-I	Generic Name	Digoxin Elixir
Medical Division	DCRDP	Drug Class	Cardiac glycoside
OCPB Reviewer	Atul Bhattaram	Indication(s)	Treatment of heart failure & atrial fibrillation
OCPB Team Leader	Patrick Marroum	Dosage Form	Elixir
		Dosing Regimen	
Date of Submission	April 14, 2003	Route of Administration	Oral
Estimated Due Date of OCPB Review	Dec 31, 2003	Sponsor	Roxane Laboratories
PDUFA Due Date	Feb 25, 2004	Priority Classification	Standard
Division Due Date	Jan 14, 2004		

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE		3		
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				

single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -	X			
solution as reference:	X			
alternate formulation as reference:	X			
Bioequivalence studies -				
traditional design; single / multi dose:	X			
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				

Pediatric development plan				
Literature References	X			
Total Number of Studies	3			

	"X" if yes	Comments
Application filable ?	X	
Comments sent to firm ?		1. To facilitate the review of this submission, it is recommended to provide electronic files for the 3 BE study reports and for the proposed labeling. 2. Also, it is recommended to provide copies and summaries of the published references that are supporting the "CLINICAL PHARMACOLOGY, Pharmacokinetics & Metabolism, and PRECAUTIONS, Drug Interactions" sections of the labeling.
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-648, HFD-110(Fromm), HFD-850(Lee), HFD-860(Mehta, Sahajwalla, Marroum).

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