CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-648

MEDICAL REVIEW(S)

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Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration
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Memorandum

DATE: 2.04

FROM: Douglas C. Throckmorton, M.D., Director
Division of Cardio-Renal Drug Products (DCRDP), HFD-110

SUBJECT: NDA 21-648
NAME OF DRUG: Digoxin Elixir, USP
SPONSOR: Roxanne Laboratories, Inc.

DOCUMENTS USED FOR MEMO:

1) Project Management summary by Ed Fromme, dated 2.23.04.
2) Patent information from section 14.0 of sponsor's submission.
3) DSI Inspection reports, from Nilufer M. Tampal, Ph.D., dated 12.11.03.
4) Medical Review by Mehul Desai, M.D., dated 12.11.03.
5) Chemistry Review by Stuart Zimmerman, Ph.D., dated 2.17.04 and 2.20.04.
6) Clinical Pharmacology and Biopharmaceutics Review, by Atul Bhattaram, Ph.D., dated 2.20.04.
7) Pharmacology Review by Belay Tesfamarium, Ph.D., dated 11.28.03.
8) DMETS review by Denise Troyer, dated 1.23.04.
9) Debarment Certification, by Elizabeth Ernst, dated 4.3.03.
10) Financial Disclosure (reviewed by Medical Officer).
11) FDA minutes of meetings with sponsor.
12) Labeling proposals by the sponsor, including slides with proposed revised indication from meeting 2.04.
13) Sponsor's ISS and ISE, and sponsor submissions through 2.18.04.

CONCLUSIONS

This memorandum constitutes the Divisional decision of approvable for the proposed marketing of the digoxin elixir product named above. This approvable action, under 505(b)(2) is based on the following:

1. The findings of safety and efficacy for the reference-listed drug (RLD).
2. Demonstration of bioequivalence of the elixir formulation with the RLD.
3. The provision by the sponsor of adequate Chemistry, Manufacturing and Controls data (CMC).
4. The submission of published references in support of the product labeling, especially the dosage and administration and those sections relevant to drug-drug-interactions.

The labeling, which is the major outstanding issue remaining to be finalized, will need to address several issues:

1. Chemistry Drug Product and Substance Issues
    a. Provide either a timeline for lowering the threshold for — in the drug substance to acceptable limits or an adequate justification for the current level — - — for a product intended for use in children.
    b. Revise the acceptance criteria for the drug product as shown in Dr. Zimmerman's review.
    c. Provide additional information regarding — in the drug product. Depending on the results, further tightening of the —, limit for this impurity may be needed:
        i. Structure.
        ii. Origin (*i.e.*, process impurity or degradent).
        iii. Levels in drug substance.
    d. Provide a revised specifications table for the drug product, incorporating all the changes listed above.

for digoxin based on the materials submitted by the sponsor and those data located by the FDA reviewers. As a result, we have two options: to deny the application (or limit the elixir use to adult dosing only) or to find a way to bridge between the available adult data on the use of digoxin to an identifiable population in children. The former is, of course, the fallback position. To accomplish the latter, there are three pieces of information that are needed:

1. A good estimate of clinical efficacy in adults.
2. A biomarker associated with adult clinical efficacy for which a relationship between concentration and effect can be derived for both children and adults.
3. An identifiable pediatric population whose disease characteristics and response to therapy (as marked by the biomarker) predict clinical benefit.

The other piece that is needed for this action, as for all 505(b)(2) actions, is demonstration of bioequivalence to the RLD. Dr. Bhattaram has reviewed these data and his conclusions (page 4 of his review) are that bioequivalence has indeed been demonstrated.

Based on the labeling for the reference-listed drug product, there are two potential populations to be discussed in turn below: congestive heart failure and atrial fibrillation. I will ultimately conclude that a pediatric population with congestive heart failure exists that have these three conditions fulfilled, but that for atrial fibrillation we have no way at present to link definable concentrations of digoxin to definable changes in any biomarker (*e.g.*, heart rate, changes in ECG parameters) in children. Additionally, it is less than clear to me that the atrial fibrillation children experience is sufficiently 'similar' to that of adults to identify a population that would be predicted to respond in similar fashion to the adults treated with digoxin.

Congestive Heart Failure

Clinical Effects of Digoxin in Adults

The clinical evidence for efficacy of digoxin in CHF comes primarily from three clinical studies: DIG, RADIANCE and PROVED (reviewed by Dr. Bhattarum starting on page 15 of his review). I will summarize them by saying that sufficient evidence exists for the efficacy of digoxin adults with congestive heart failure. There is no net benefit of digoxin on mortality.

Effects of Digoxin on Biomarker (Contractility) in Adults and Children, Concentration-Effect Relationship

The effects of digoxin on cardiac contractility in adults is discussed beginning on page 16 of Dr. Bhattarum's review. He concludes that increased digoxin concentrations caused an increase in left ventricular ejection time.

The effects of digoxin on cardiac contractility in children is also discussed in both of the primary reviews (*e.g.*, Dr. Desai's review pages 25-34). Here, the most useful data come from studies looking at the very young (< 2 years of age), but document an acute improvement in contractility following IV administration of digoxin. The reviewers correctly point out that these studies were not always done in children with congestive heart failure related to impaired contractility. While an issue, the sponsor has argued (and I agree) that the demonstration of improved contractility in one pediatric population provides strong rationale for believing digoxin has that effect in all relevant pediatric populations.

Dr. Bhattarum also writes extensively about the relationship between digoxin concentration and changes in contractility. It is an essential part of the argument that we be able to describe the concentration-effect relathionship for digoxin in children for changes in contractility, in order to provide adequate instructions for use. He concludes that the concentrations used in children are on the 'flat' portion of the dose-response curve for similar effects in adults (see page 26). He argues that we cannot know whether lower concentration would also be effective (but seems likely). He is also concerned about the use of the older assays for digoxin, which captured other 'endogenous' digoxin-like products, making the assessments of the concentration-effect more problematic. Here, I disagree. While recognizing the limitations of the data (eloquently detailed by both reviewers) we can, at the end of the day, conclude that a definable concentration of digoxin will have a describable effect on the biomarker of interest in children. That additional information, especially about the use of lower concentrations, would be useful is undeniable, and the potential gains with regard to safety seem attractive. The one place this concern is paramount, I believe, is in the use of the product in the very small infants less than 2 years of age. Here, given their fragility and the extreme toxicities of digoxin, additional information is needed before describing dosing for them.

Clinical Outcomes in Pediatric Population with Congestive Heart Failure

There are not adequate clinical data in children with congestive heart failure, although the available data are suggestive of some benefits. The studies discussed Dr. Desai starting on page 25 of his review provide safety as well as providing the data linking serum concentrations of digoxin to changes in contractility.

The final question is whether there is an identifiable pediatric population with clinical characteristics that are similar enough to the adult population that we can rely on the biomarker to inform clinical efficacy. In a series of teleconferences with the sponsor, and in submissions to the NDA, experts from the company have argued that while much of the heart failure in children comes about not from impaired contractility but from anatomic defects (*e.g.*, patent ductus arteriosus), a population of children whose primary defect is contractility exists. They also assert that the fraction of children with this defect rises from infancy through early childhood as the fraction of children with surgically remediable disease declines. In this population, then, we have sufficient data linking the adult clinical data on the use of digoxin in heart failure to changes in contractility suggesting clinical efficacy. While far short of the desired clinical data, there is a sufficient database to label this elixir for use in these children with congestive heart failure.

Atrial Fibrillation

For atrial fibrillation, the situation is significantly different. First, while there are data on the clinical effects of digoxin in atrial fibrillation in adults that can be paired to effects on a plausible biomarker (changes in heart rate). We also have information on the concentrations of digoxin in this population. We lack, however, two critical pieces for the pediatric population. First, while there are small studies looking at effects on heart rate, they are not paired to concentrations, so that we can't describe the concentrations of digoxin necessary to provide these effects in children. A second critical lesion is that the causes of atrial fibrillation differ significantly in the adult and pediatric populations. Given the, we can't use a biomarker like heart rate to provide a link to the adult data, even if we had concentration data, and adequate clinical data are needed to support digoxin's use in the pediatric population. Absent these data (and Dr. Desai concludes that this is the case), no indication for the use of digoxin in children with atrial fibrillation can be supported.

MEDICAL REVIEW OF SAFETY

No new safety issues were identified by the reviewer that necessitates changes to the label. The toxicities of digoxin described in the publications for both adults and children are similar. These data are inadequate to determine whether increased sensitivity to any of these toxicities exists for one or more sub-group of children.

SUMMARY

Pending resolution of the issues identified in the conclusions above, largely revolving around labeling, this product is approvable. The labeling

LABELING

The major issues related to labeling are outlined in my conclusions above.

PEDIATRICS

There are a number of unanswered questions concerning the safe use of digoxin, especially in the children less than 2 years of age. Given the disconnect between the doses used clinically and the predicted kinetics of digoxin in these small, fragile children, labeling this product for use in children <2 will require additional information than what we have at present. The sponsor is to be encouraged to conduct such studies. The use of this formulation in children with atrial fibrillation is similarly not established. Here the lesion is a lack of demonstrated relationship between concentration and clinical effect. Again, additional data are to be encouraged to close this gap and provide labeling for the use of this formulation in children with atrial fibrillation.

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/s/

Doug Throckmorton
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MEDICAL OFFICER

Division of Cardio-Renal Drug Products

Addendum to Medical Officer Review

Date: 6 January 2004

Reviewer: Mehul Desai, M.D. , Medical Officer
Division of Cardio-Renal Drug Products, HFD-110

Subject: Addendum to NDA#21-648 Medical Officer Review re: Financial disclosure info.

Sponsor: Roxanne Laboratories (Boehringer Ingelheim)

This addendum updates the evaluation of financial disclosure. The sponsor did not conduct clinical studies on the efficacy or safety of digoxin. They did conduct a PK study assessing the single dose bioequivalence of Roxanne's Digoxin Elixir to that of Glaxo SmithKline's Lanoxin Tablets. For this study, a copy of the financial certification form (Form 3454) was submitted by the sponsor for the 2 principal investigators.

Mehul Desai, M.D. Medical Officer
Division of Cardio-renal Drug products, HFD-110

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/s/

Mehul Desai
1/13/04 02:41:53 PM
MEDICAL OFFICER

CLINICAL REVIEW

Clinical Review Cover Sheet

Digoxin Elixir
NDA # 021-648

Mehul Desai, M.D.

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Abbreviations

CHF = Congestive heart failure
PDA = patent ductus arteriosus
ASD = atrial septal defect
VSD = ventricular septal defect
BWG = Bland-White-Garland syndrome
SVT = supra-ventricular tachycardia
WPW = Wolf Parkinson White syndrome
NSR = normal sinus rhythm
DD = Digitalizing (Loading) dose
MD = maintenance dose
PVC's or VPB's = premature ventricular contractions/ ventricular premature beats
AV block = atrio-ventricular block
VT = ventricular tachycardia

Clinical Review for NDA 21-648

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Roxane Laboratories, Inc. has submitted a 505(b)(2) New Drug Application for Digoxin Elixir 0.05 mg/mL. Digoxin Elixir is currently marketed but lacks an "official" associated NDA. Through a Federal Register Notice in November 2000, the Agency mandated that all manufacturers of Digoxin Elixir submit a NDA to allow continued marketing of their respective products.

Currently, there are two oral formulations of digoxin that are marketed: elixir and tablet. The tablet formulation is approved (NDA # 20-405) while the elixir formulation is not approved. Both formulations contain information on pediatric dosing and the dosing instructions are similar but not identical between the two formulations. **It is important to note that the basis for pediatric dosing instructions in the approved, tablet formulation is not clear.** As a result, the unapproved elixir can not rely on the tablet formulation to support pediatric dosing instructions.

In this supplemental NDA, the Agency is seeking evidence of efficacy and safety justifying the use of digoxin in pediatric populations. The need to justify the efficacy and safety of digoxin elixir in pediatric populations is relevant because it is likely to be the population that will be the primary recipient. The sponsor has submitted references from the peer reviewed medical literature that they believe support their proposed pediatric dosing and administration instructions in the label. The sponsor has submitted relatively few studies of the use of digoxin in adults because the role in adult patients has been adequately characterized from previous studies (e.g. DIG study[1]).

A careful review of the submitted references along with an independent search of the peer reviewed medical literature does not support the current proposed labeling in pediatric populations. There are no randomized, placebo controlled, blinded studies, evaluating outcomes of clinical importance. Many of the studies of the studies done in congestive heart failure have major flaws e.g. small numbers of subjects, no appropriate control groups, lack of blinding, evaluating endpoints of questionable clinical relevance (e.g. echocardiographic endpoints), etc. No prospective studies have been identified that evaluate the role of digoxin in pediatric arrhythmias. The studies of the use of digoxin in pediatric arrhythmias that have been identified are all retrospective.

A lack of clear evidence of efficacy in pediatric populations along with a real risk of toxicity, makes approval based on existing data very problematic. It may be possible for the sponsor to conduct well-designed studies from which the Agency could better understand the doses that should be used and identify the indications for which such doses should be used. Please see "Recommendation on Phase 4 Studies and/or Risk Management Steps" below for further details.

In summary, the quality of pediatric studies from the literature does not provide conclusive evidence of efficacy or safety based on standards used by the Food and Drug Administration today. The majority of studies in the literature are uncontrolled, unblinded studies looking at endpoint that are not clinically meaningful or are retrospective studies.

I believe that there are 3 available options. The first option is to do nothing which I don't believe supports the Agency's mission of ensuring that safe and effective drugs are on the market. The process of reviewing the peer reviewed medical literature has shown that there is no justification for the current digoxin elixir labeling in a pediatric population. It makes little sense for the Agency to allow marketing of a drug for a population in whom efficacy is not clearly established and for which the risk of toxicity is real.

The second option is to remove dosing recommendations for pediatric populations and explicitly state in the label that there are no adequate data in the peer reviewed medical literature that support efficacy in that population. In this scenario, digoxin elixir would be approved for use in adult patients that can't swallow (e.g. intubated patients, patients with G-tube in place secondary to stroke or upper GI pathology) in which case safety and efficacy information could be referenced from the tablet. This could be an acceptable alternative provided that pediatricians do not begin to use digoxin elixir "off-label".

The third option is to have the Sponsor conduct adequate and well controlled trials that conform to the standards used by the Agency today. I believe this is the best option but one that will likely be challenging. Some of the barriers to completing such a trial would be convincing parents to enroll their children in a placebo controlled trial. From an ethical perspective, this might be possible because there is inadequate data that digoxin has efficacy in this population. The difficulties of doing such a clinical trial in children would involve choosing appropriate endpoints to use. In adults, digoxin is indicated to improve symptoms of heart failure and to control ventricular response rate in patients with chronic atrial fibrillation. Symptomatic endpoints would be nearly impossible to adequately evaluate in a pediatric population involving neonates or toddlers. Reducing hospital stay could be a possible endpoint to study. With respect to atrial fibrillation, it is a rather uncommon arrhythmia in this population. In considering a pediatric clinical trial for heart failure or atrial fibrillation, the key question would be whether it is practical to enroll enough pediatric patients so that there would be adequate power to detect an effect. A pharmacokinetic/pharmacodynamic study could be an option except for the fact that the pathophysiology of heart failure is sufficiently different in adults and

children to make extrapolation very difficult. A PK/PD study could be an option if sufficient numbers of children with atrial fibrillation could be enrolled. In this scenario, heart rate could serve as a potential surrogate.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

N/A

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Roxane Laboratories, Inc (RLI) has not conducted any original clinical studies of efficacy or safety using Digoxin Elixir. They rely exclusively on the peer-reviewed medical literature to support the indications, dosing, administration, and safety aspects of the proposed label.

RLI has submitted 3 human pharmacokinetic/bioequivalence studies as part of this NDA. Two of these studies were fed and fasting bioequivalence studies using Glaxo-Smith-Kline's (GSK's) Lanoxin Tablets 0.25mg as a reference. The studies showed that RLI's elixir is bioequivalent to GSK's tablet in terms of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$.

B. Efficacy

In this review, I primarily focus on the efficacy and safety of digoxin in pediatric populations because the formulation being considered for approval will be primarily targeted at children. Based on the references submitted by the sponsor and an independent review of the medical literature, there is inadequate evidence to support effectiveness in pediatric populations for the indications of congestive heart failure and/or arrhythmia management. Given the limited resources available, I have not reviewed every available study. The studies I have reviewed are representative of the type of studies that exist in the peer reviewed medical literature. All the studies have major flaws (e.g. retrospective study design, lack of randomization, lack of appropriate control groups, lack of blinding, or studying endpoints of little clinical relevance).

C. Safety

It would be ideal to better characterize the safety profile of digoxin in pediatric populations although few would argue that the risk of digoxin associated toxicity is real. Some of the manifestations of digoxin toxicity seen in adult patients (e.g. nausea, visual changes, dizziness, mental status changes) are difficult to illicit in pediatric populations that have not yet developed the skills to vocalize complaints. Often times, electrocardiographic changes are the primary presentation of digoxin toxicity. Several studies that are detailed below suggest that toxicity with digoxin is dose-dependant. Some of the reported manifestations of toxicity include sinus node depression, atrioventricular block (2^{nd} degree), ventricular arrhythmias (e.g. ventricular fibrillation), premature ventricular contractions, and paroxysmal atrial tachycardia. Non-electrocardiographic toxicity that has been reported includes vomiting and poor feeding.

D. Dosing

Because of the lack of quality data showing efficacy in pediatric populations, the current recommendations for dosing Digoxin elixir are based on the desire to achieve concentrations within the adult therapeutic range of 1 to 2 ng/mL. The rationale for this is not entirely clear. Doing appropriately designed studies could lead to better dose selection and minimize potential for adverse drug reactions.

E. Special Populations

This review of digoxin elixir is primarily focused on evaluating the efficacy and safety in a special population, namely pediatric.

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Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Name of drug: Digoxin Elixir 0.5mg/mL
Drug Class: Cardiac glycoside
Proposed indication: Heart failure, Atrial fibrillation
Dose:

Adults: 3 µg/kg/day

The proposed dosing regimen shown above can be compared and contrasted to the dosing regimens in the existing labels by referring to Appendix Tables 1 and 2 in the Appendix.

B. State of Armamentarium for Indication(s)

Many therapeutic options are available for the treatment of congestive heart failure in adults (e.g. digoxin, diuretics, ACE-inhibitors, β-Blockers). Many of these therapies are used in pediatric populations, although there is relatively less efficacy data compared to adults. It is difficult to extrapolate findings from adult heart failure studies to pediatric populations because the pathophysiology is markedly different. The main causes of CHF in children that live in developed countries include 1) congenital heart disease 2) cardiomyopathy 3) myocardial dysfunction after repair of heart defects[2]. In contrast, the main etiologies of heart failure in adults are related to coronary heart disease and hypertension.

Similar to congestive heart failure, many therapeutic options are available for arrhythmia management in adults (e.g. β-blockers, calcium channel blockers, amiodarone, digoxin, procainamide, propafenone, sotalol, etc.) Some of these therapies have also been used in children although the efficacy is not as well

defined as in adults. Digoxin, in particular, is indicated for the control of the ventricular response rate in patients with chronic atrial fibrillation. However, atrial fibrillation is a rare arrhythmia in infants and children[3]. When this arrhythmia is seen, it is usually in the setting of surgical repair of congenital heart disease involving the atria. Other types of supra-ventricular tachycardias are much more common in pediatric patients (e.g. atrio-ventricular reentrant tachycardia/WPW and atrial flutter)[4]. Atrial fibrillation is the only type of arrhythmia for which digoxin is labeled in adults.

C. Important Milestones in Product Development

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 was submitted for a different formulation of digoxin, that of 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 and PROVED studies that were randomized, parallel group, placebo-controlled withdrawal trials. In 1997, after the completion of the DIG study, the labeling to Lanoxin was updated.

D. Other Relevant Information

N/A

E. Important Issues with Pharmacologically Related Agents

Digitoxin and ouabain are cardiac glycosides that possess similar actions to digoxin. They differ from digoxin in terms of pharmacokinetics and metabolism. They are not commercially available in the U.S.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Please refer to Biopharmaceutics Review for details.
I provide here only a brief synopsis.

Fasting Bioequivalence study: comparator drug was Lanoxin (Glaxo Smith Kline)

This was an open label, randomized, uncontrolled, 2 period, 2 sequence design in healthy volunteers (fasted). Subjects received a single oral dose of 1mg on 2 occasions. A total of 28 volunteers were enrolled with 25 completing both study periods. They ranged in age from 20 to 45 years. Results are as follows:

Parameter	Roxane Digoxin elixir	Lanoxin tablet
C_{max} (ng/mL)	2.08 ± 0.63	1.93 ± 0.64
T_{max} (hr)	0.75	1.00
AUC_{0-t} (hr*ng/mL)	29.4 ± 10.1	31.8 ± 9.37
AUC_{∞} (hr*ng/mL)	34.9 ± 14.0	37.5 ± 9.53
$T_{½}$ (hr)	32.3 ± 6.9	32.4 ± 6.54

	Ratio (%)	
Parameter	Point estimate	90% confidence interval
C_{max}	107.9	95.8 → 121.5
AUC_{0-t}	90.2	83.6 → 97.3
AUC_{∞}	95.0	87.5 → 103.2

Fed Bioequivalence study: comparator drug was Lanoxin (Glaxo Smith Kline)

This was an open label, randomized, uncontrolled, 2 period, 2 sequence design in healthy volunteers (fed). Subjects received a single oral dose of 1mg on 2 occasions. A total of 26 volunteers were enrolled with 25 completing both study periods. They ranged in age from 18 to 45 years. Results are as follows:

Parameter	Roxane Digoxin elixir	Lanoxin tablet
C_{max} (ng/mL)	2.53 ± 0.68	2.47 ± 0.95
T_{max} (hr)	1.0	1.75
AUC_{0-t} (hr*ng/mL)	40.7 ± 13.2	39.0 ± 11.9
AUC_{∞} (hr*ng/mL)	45.5 ± 13.7	47.0 ± 15.0
$T_{½}$ (hr)	31.0 ± 6.67	29.4 ± 7.93

	Ratio (%)	
Parameter	Point estimate	90% confidence interval
C_{max}	105.2	91.8 → 120.7
AUC_{0-t}	103.4	92.1 → 116.1
AUC_{∞}	102.1	79.6 → 130.9

From the data shown above, Roxane Laboratories Digoxin elixir was bioequivalent to Lanoxin under fasting conditions with respect to both C_{max} and AUC. However, it was not bioequivalent in nominal terms, under fed conditions with respect to AUC ∞. The clinical relevance of this difference under fed conditions may merit consideration only after efficacy of this formulation is characterized in pediatric populations.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

The kinetics of digoxin can be described by a two-compartment model with a relatively rapid *alpha* phase and a much slower *beta* phase. The bioavailability of digoxin elixir (Lanoxin pediatric solution, Burroughs Wellcome Ltd.) has been evaluated in neonates. The mean bioavailability of digoxin elixir was estimated to be 72% in a study of 4 term neonates with heart failure[5].

The pharmacokinetics of digoxin is quite variable during the process of pediatric development (from neonate to infant and ultimately to children). Figure 1 below, obtained from a review article by Hastreiter et. al., illustrates this variability with respect to half-life and additionally the primary pharmacokinetic parameters of clearance and volume of distribution[6].

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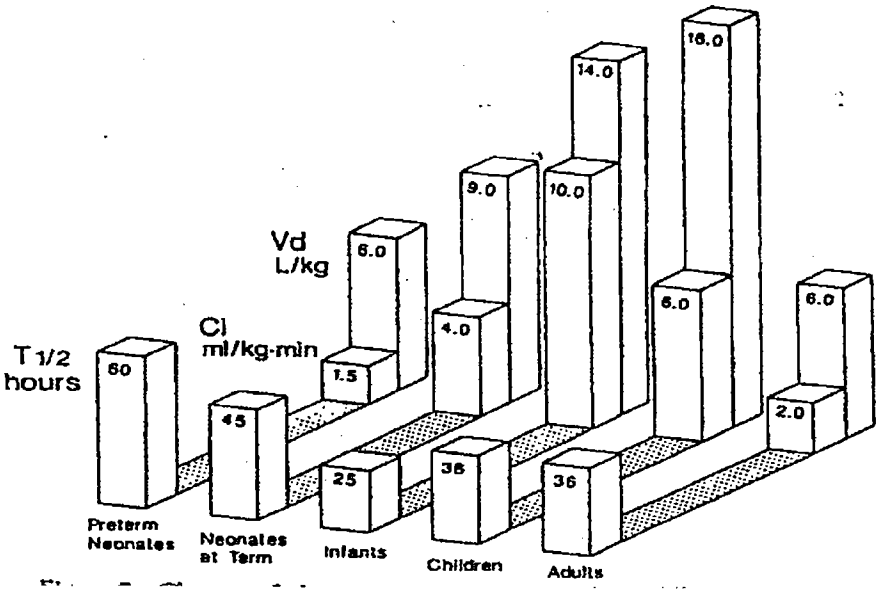
Figure 1: Changes in pharmacokinetic parameters of digoxin as a function of stage of pediatric development: plasma half-life ($T_{½}$), volume of distribution (V_d), and Body clearance (CL).



The weight adjusted digoxin clearance is lowest among pre-term neonates. Term neonates have a higher weight adjusted clearance on average relative to pre-term neonates. Infants have the highest weight adjusted clearance. The weight-adjusted digoxin clearance progressively declines from infancy to childhood and on into adulthood and is likely due to a plateau in the renal function that occurs in infancy. It should be recognized that although the weight-adjusted clearance in adults according to the figure above is low, clearance on an absolute basis (not adjusted for weight) is highest in this group.

Table 1 below shows pharmacokinetic parameters from a review article by Wells et. al.[7] Although the patterns of pharmacokinetic changes are consistent to those in Figure 1, this table is useful because it displays a range of values and thus gives us some idea as to the extent of variability within each pediatric subpopulation.

Table 1: Pharmacokinetic parameters for digoxin in children[a]

Population	Apparent volume of distribution (L/kg)	Total body clearance (mL/min/kg)	Elimination half-life (hours)
Premature newborns	3.5 – 6.0	0.75 – 1.4	35 – 170
Term newborns	5.0 – 10.0	1.7 – 2.9	35 – 70
Infants (2 – 24 months)	8.0 – 16.3	2.7 – 10.0	18 – 36
Children (2 – 10 years)	8.6 – 12.8	2.8 – 6.0	36
Adults	5 – 7.5	1.5 – 4	36 – 50

[a]The data in this table was obtained from reference number 7.

Digoxin tends to concentrate in heart tissue to a greater extent in infants than in adults as shown in Table 2 below[8]. In this study, there were a total of 12 infants with a median age of 12 months. The median age of the 17 adults in this study was 58 years. All patients in this study received oral digoxin for a minimum of 1 month for congenital or acquired heart disease and were scheduled for cardiac surgery utilizing cardiopulmonary bypass.

Table 2: Comparison of mean digoxin dose, mean concentrations of digoxin in the heart and mean serum digoxin concentrations in infants versus adults[a].

	Mean digoxin dose (µg/kg/day)	Mean RAA[b] conc. (ng/g of wet weight)	Mean serum digoxin conc. (ng/mL)	Mean RAA:serum ratio
Infants	11.96 ± 0.91	211.8 ± 72.1	1.27 ± 0.25	149 ± 31
Adults	3.36 ± 0.21	35.1 ± 7.7	1.30 ± 0.11	28 ± 5

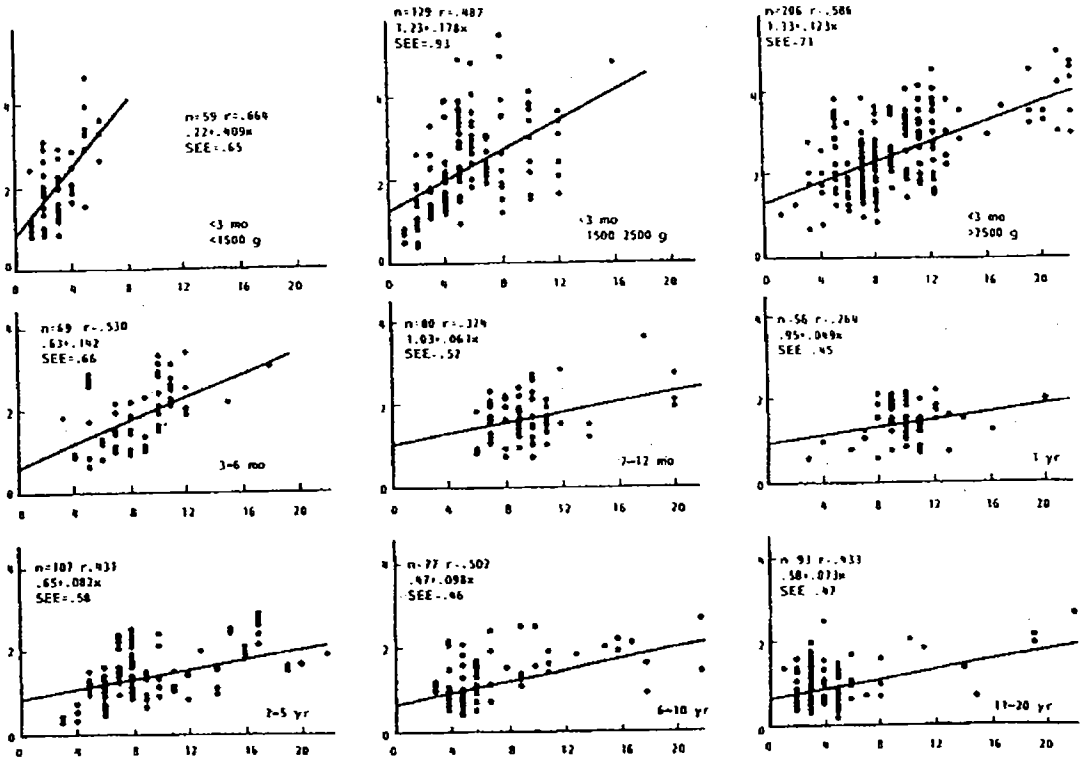
[a]The data in this table were obtained from reference number 8

[b]RAA = right atrial appendage

There is a relatively poor correlation between the dose of digoxin administered and the steady-state plasma concentrations of digoxin achieved as shown in Figure 2 below[9]. The plots in the Figure below were derived from studying 478 pediatric patients of varying ages that were free of acute illnesses, severe electrolyte imbalances and renal failure. These patients received an oral

formulation of digoxin during this prospective clinical trial and plasma concentrations were measured at steady state.

Figure 2: Plots of digoxin plasma concentration (ng/mL on y-axis) versus dosage (μg/kg/day on x-axis) for various age and weight groups of infants and children who received digoxin orally. Each panel displays the specific age and/or weight group on the bottom right hand corner. Each panel also displays the regression line of best fit and corresponding correlation coefficients.



Measurement of digoxin in plasma is generally done via a RIA (radio-immunoassay) technique. Plasma measurements are routinely obtained in clinical settings because digoxin is considered a narrow therapeutic index drug. It is important to recognize that an elevated digoxin concentration in plasma can be a non-specific finding that is not always associated with a drug overdose. Elevated levels may be seen due to inappropriate sampling (e.g. collecting plasma sample

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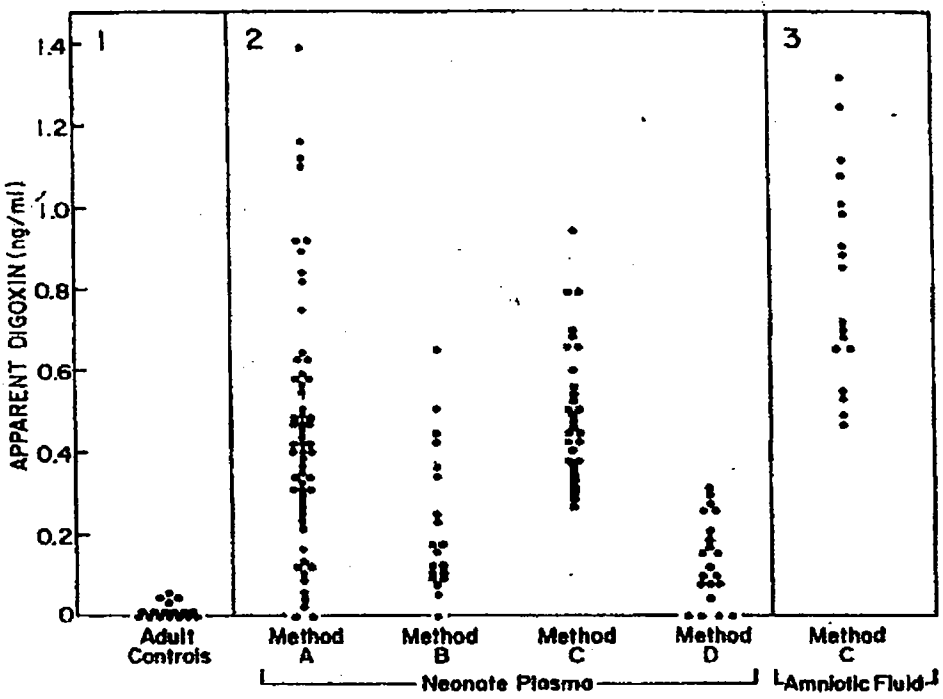
relatively soon after drug administration), renal failure, hepatic failure, concomitant medications (e.g. spironolactone) or digoxin like immunoreactive substances (DLIS)[10, 11, 12].

In the early 1980's Valdes et. al. reported on the detection of DLIS in the plasma of neonates, infants and also in amniotic fluid[13]. He measured the plasma of over 135 normal newborn infants 2 to 4 days of age (not receiving digoxin therapy) for the presence of "apparent digoxin." As seen in Figure 3 below, "apparent digoxin" concentrations approaching and overlapping the therapeutic concentration range were detected. The range of "apparent digoxin" concentrations varied with the RIA method used for measurement.

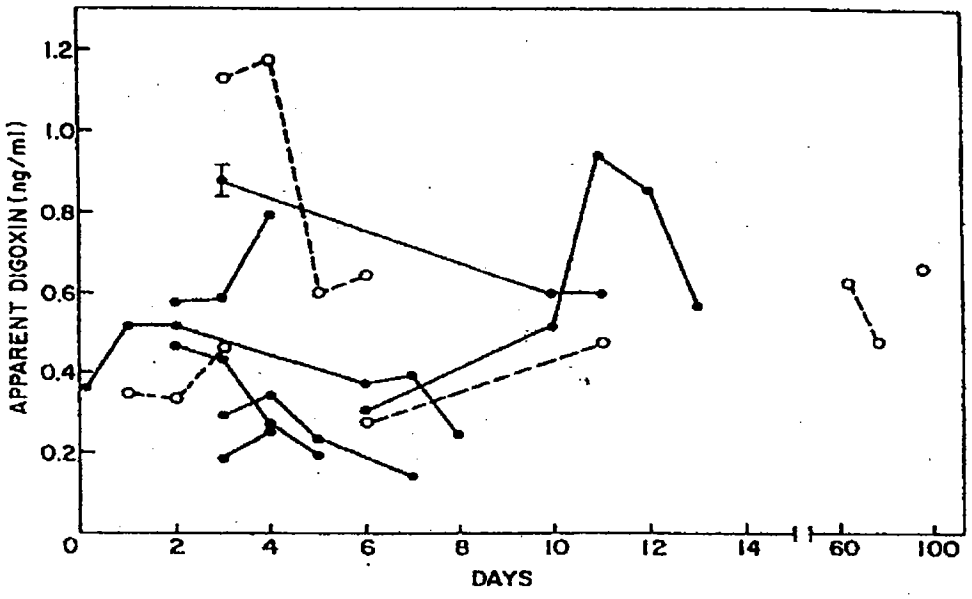
Figure 3: Apparent digoxin concentration measured in healthy adult controls, neonates by different RIA methods (method A to D), and in amniotic fluid. All data points represent different individuals.



DLIS has implications with respect to how reliable the published pharmacokinetic data in the neonatal population are prior to the recognition of this phenomenon. Many pharmacokinetic studies with digoxin were done before the recognition of DLIS in the 1980's.

Figure 4 below, also from the work of Valdes et. al. shows the "apparent digoxin" concentrations as a function of time in 12 infants[13].

Figure 4: Apparent digoxin concentrations over time in plasma of 12 infants.



In his manuscript, Valdes states that the presence of DLIS is not limited to neonates but can also be seen in infants well over 60 days of age. In his manuscript, he questions the reliability and clinical utility of digoxin RIA measurements on the plasma of neonates or infants.

A review article by Hastreiter et. al. states that DLIS levels as high as 4.1 ng/mL have been reported in the literature[2]. It is stated that variability in the plasma levels of DLIS are probably due to RIA kit to kit variability.

Newer digoxin immunoassay techniques seem to show improved specificity (less DLIS detection) relative to older immunoassays[14, 15]. Often, studies of these newer methodologies are sponsored by their innovators. Results of such studies could be biased if comparisons of the newer and older methodologies are not done in a blinded manner.

B. Pharmacodynamics

Digoxin's actions are mediated through its effects on sodium-potassium ATPase enzyme. This enzyme maintains the intracellular milieu throughout the body by moving sodium ions out of cells and potassium ions in. By inhibiting this enzyme, digoxin produces increased availability of intracellular calcium and

in turn increases inotropy and automaticity while decreasing conduction velocity. Increased availability of intracellular calcium in the renal tubules produces increased natriuresis. Some other effects of digoxin include parasympathetic stimulation of the autonomic nervous system with effects on the sino-atrial and atrio-ventricular nodes. There are additional effects of digoxin that are not fully discussed here. The point I would like to make is that digoxin has effects on both the mechanical and electrical functioning of the heart.

It is important to recognize that mechanical effects of digoxin on the heart may not always correlate with patient symptoms or clinical response. Using pharmacodynamic surrogate markers in heart failure to predict symptomatic or clinical response has proven difficult. Using heart rate as surrogate of digoxin's effects on the electrical conduction system is useful for arrhythmias such as atrial fibrillation. However, as discussed earlier, this type of arrhythmia is uncommon in pediatric patients.

IV. Description of Clinical Data and Sources

A. Overall Data

This NDA submission by Roxane Laboratories is in effect a "paper NDA" relying exclusively on the peer reviewed medical literature to provide justification for current pediatric labeling. Roxanne has submitted these references because, in their opinion, the submitted references provide the best available evidence for determining safety and efficacy. Roxanne obtained assistance from physician consultants active in pediatric cardiology in collecting and reviewing the references. A total of 251 references were submitted. From these 251 references 30 were summarized and put in Table format.

There is a substantial amount of literature regarding the use of digoxin in the pediatric population. The majority of data on digoxin was collected during the 1960's, 1970's and 1980's. Relatively little data is available from the past 5 to 10 years relating to the pediatric use of digoxin. The majority of the prospective studies have evaluated small numbers of patients (e.g. 40 or less). In almost all cases, major flaws exist: lack of control groups, lack of blinding, studying endpoints of limited clinical significance. I could find no prospective studies available for the use of digoxin in the treatment of pediatric arrhythmias. All the studies I evaluated were retrospective.

It would require significantly more time and resources than are available to evaluate every available pediatric study for safety and efficacy of digoxin. The studies I've included in this review are representative of the quality of evidence that exists regarding the efficacy and safety of digoxin in a pediatric population.

B. Tables Listing the Clinical Trials (by indication)

Table 3: List of studies in the peer reviewed medical literature in supporting the indication of Congestive Heart Failure (CHF).

Study Title	Population	Study Design[a]	Endpoints	Reference
"Effect of digoxin on contractility and symptoms in infants with a large ventricular septal defect."	Infants (n = 36)	Prospective, unblinded; Control group present	Serum digoxin levels; Echocardiographic	Kimball TR et. al. Am J Cardiol. 1991;68:1377-82[16].
"Effect of digoxin on left ventricular contractility in newborns and infants estimated by echocardiography."	Newborns and infants (n = 17)	Prospective, uncontrolled, unblinded,	Plasma digoxin levels; Echocardiographic	Hofstetter R et. al. Eur J Cardiol. 1979;9:1-11[17].
"The use of digitalis in infants and children: a clinical study of patients in congestive heart failure."	"Children" (n = 41; age range 1 month to 14 years)	Prospective, uncontrolled, unblinded	Clinical response judged as "good", "fair" or "poor" based on clinical signs and symptoms	Nadas AS et. al. N Engl J Med. 1953;248:98-105[18].
"Noninvasive assessment of left ventricular function related to serum digoxin levels in neonates."	Neonates (n = 18)	Prospective, uncontrolled, unblinded	Serum digoxin levels, echocardiographic	Sandor GG et. al. Pediatrics. 1980;65:541-6[19].
"Effects of digoxin in infants with congested circulatory state due to a ventricular septal defect."	Neonates (n = 21)	Prospective, uncontrolled, unblinded	Echocardiographic, Biomarker (Na/K ATPase activity), clinical assessments	Berman W et. al. N.Engl.J Med. 1983;308:363-66[20].
"Further evidence suggesting a limited role of digitalis in infants with circulatory congestion secondary to large ventricular septal defect."	Infants (n = 41)	Prospective, uncontrolled, unblinded	Hemodynamic measurements via catheterization; Serum digoxin concentrations	Seguchi M et. al. Am J Cardiol. 1999;83:1408-11, A8[21].
"Digoxin therapy and left ventricular performance in premature infants with patent ductus arteriosus."	Premature neonates (n = 16)	Prospective, uncontrolled, unblinded	Serum digoxin levels, echocardiographic	Lundell BP et. al. Acta Pediatr Scand 1983; 72: 339-43[22].

[a]The specific study design was not always described in many of the manuscripts. The description provided represents the best assessment by this reviewer.

Table 4: List of studies in the peer reviewed medical literature in supporting the indication of Arrhythmia.

Study Title	Population	Study Design[a]	Endpoints	Reference
"Re-entrant supraventricular tachycardia in infancy: current role of prophylactic digoxin treatment."	Neonates and infants (n = 26)	Retrospective	SVT recurrence	Pfammatter JP et. al. Eur J Pediatr. 1998;157:101-6[23].
"Supraventricular tachycardia in children: clinical features, response to treatment, and long-term follow-up in 217 patients."	"Children" (n = 217)	Retrospective	SVT recurrence	Garson A et. al. J Pediatr. 1981;98:875-82[24].
"Wolff-Parkinson-White syndrome and supraventricular tachycardia during infancy: management and follow-up."	"Children" (n = 90)	Retrospective	Recurrent arrhythmia	Deal BJ et. al. J Am Coll.Cardiol. 1985;5:130-135[25].
"Atrial flutter in the young: a collaborative study of 380 cases."	"Children" (n = 380)	Retrospective	Abolition of arrhythmia	Garson A Jr et. al. J Am Coll Cardiol. 1985;6:871-8[26].
"Paroxysmal supraventricular tachycardia in infancy and childhood."	Infants (n = 39)	Retrospective	Termination of tachycardia	Lubbers WJ et. al. Eur J Cardiol. 1974;2:91-99[27].
"Atrial automatic tachycardia in children."	Children (N = 9)	Retrospective	Abolition of arrhythmia, restoration of sinus rhythm, or heart rate control	Koike K et. al. Am J Cardiol. 1988;61:1127-30[28].
"Atrial flutter in the human fetus: diagnosis, hemodynamic consequences, and therapy"	Fetus (in utero) (n = 10)	Retrospective	Restoration of normal sinus rhythm	Soyeur DJ. J Cardiovasc Electrophysiol. 1996;7:989-98[29].
"Natural history of isolated atrial flutter in infancy"	Neonates (n = 9)	Retrospective	Restoration of normal sinus rhythm	Mendelsohn A. et. al. J Pediatr. 1991;119:386-91[30].

[a]The specific study design was not always described in many of the manuscripts. The description provided represents the best assessment by this reviewer.

C. Postmarketing Experience

This review is in effect a review of the post marketing experience with all the data coming from the peer reviewed medical literature.

D. Literature Review

See Section IVA. This NDA is in effect a literature review.

V. Clinical Review Methods

A. How the Review was Conducted

The sponsor submitted 251 references from the peer reviewed medical literature in support of NDA 025-648 for Digoxin elixir. The majority of the submitted references deal with the use of this drug in a pediatric population. From these 251 references, 30 were summarized in tabular form. These 30 references, presumably, represent the best available evidence in support of digoxin's adequate instructions for use.

All the original references submitted by the sponsor were read - some in more details than others. The articles were separated based on those showing evidence of efficacy, safety or both. References for a more detailed review were selected that were felt to be representative of the type of data that is available. Even though every single efficacy or safety study available has likely not have been reviewed, I don't believe the addition of those studies would not substantially alter the conclusions of this review.

The focus of this review is primarily that of assessing the quality of data that exists on the use of digoxin in pediatric populations. As part of this review, an attempt was made to gain a better understanding of how specific pediatric dosing instructions were included in the Lanoxicaps label. After a review of the Division Files, it was concluded that the pediatric labeling in the Lanoxicaps label wasn't specifically evaluated with respect to strength of evidence as part of the NDA in 1994.

B. Overview of Materials Consulted in Review

Literature references

C. Overview of Methods Used to Evaluate Data Quality and Integrity

Not applicable as I did not have access to the primary data.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

Not applicable

E. Evaluation of Financial Disclosure

Not applicable

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

The references in the peer reviewed medical literature do not provide adequate evidence of efficacy for either the indication of congestive heart failure or for cardiac arrhythmias.

For the indication of congestive heart failure, 7 studies from the peer reviewed medical literature were reviewed that are representative of the quality of available data. None of these fulfill the Agency's criteria of adequate and well controlled studies by today's standards. Each of the studies has significant flaws. For example a study by Kimball et. al.[16] was prospective by design and had a control group. However, the patients enrolled had dissimilar baseline characteristics. In addition, the control group consisted of patients without heart disease while the treatment group consisted of patients with clinically significant congenital heart disease. Many of the studies that were reviewed had as their endpoints echocardiographic assessments (e.g. Hofstetter et. al.[17], Sandor et. al[19], Berman et. al.[20], etc.). A major limitation of echocardiographic assessments is that they often don't correlate well with clinical endpoints. One study by Nadas et. al.[18] evaluated clinical outcomes, however the major flaws in this study was that there was no control group and clinical assessments were unblinded.

For the indication of arrhythmia treatment, 8 studies were reviewed. Most of the arrhythmias evaluated in the patients involved in these studies were supraventricular (e.g. atrial flutter most common). All 8 of these studies were retrospective. Very few conclusions, if any, can be drawn from this type of study design. More detailed descriptions of these studies are in the following section.

B. General Approach to Review of the Efficacy of the Drug

The sponsor submitted 251 references supporting the use of digoxin in pediatric populations. A set of 7 studies supporting an efficacy claim for congestive heart failure $\pm$ congenital heart disease were identified and 8 studies supporting efficacy of digoxin in supraventricular tachycardia were also identified. These studies

were reviewed in detail and are summarized below. References submitted by the sponsor were not all reviewed in equal depth. The references that were reviewed, were felt to be representative of the types of studies that are available in support of efficacy.

C. Detailed Review of Trials by Indication

Congestive Heart Failure

Study title: "Effect of digoxin on contractility and symptoms in infants with a large ventricular septal defect" [16]

Population: 19 infants, median age = 2.5 ± 3.1 months, median weight = 4.9 ± 1.9 kg, symptomatic CHF secondary to ventricular septal defect (VSD)

Design: Prospective, Unrandomized, Unblinded Study; A control group was present and consisted of 17 infants without heart disease (median age = 5 months, median weight = 8 kg). There were 4 periods of evaluation consisting of symptom evaluation and echocardiography

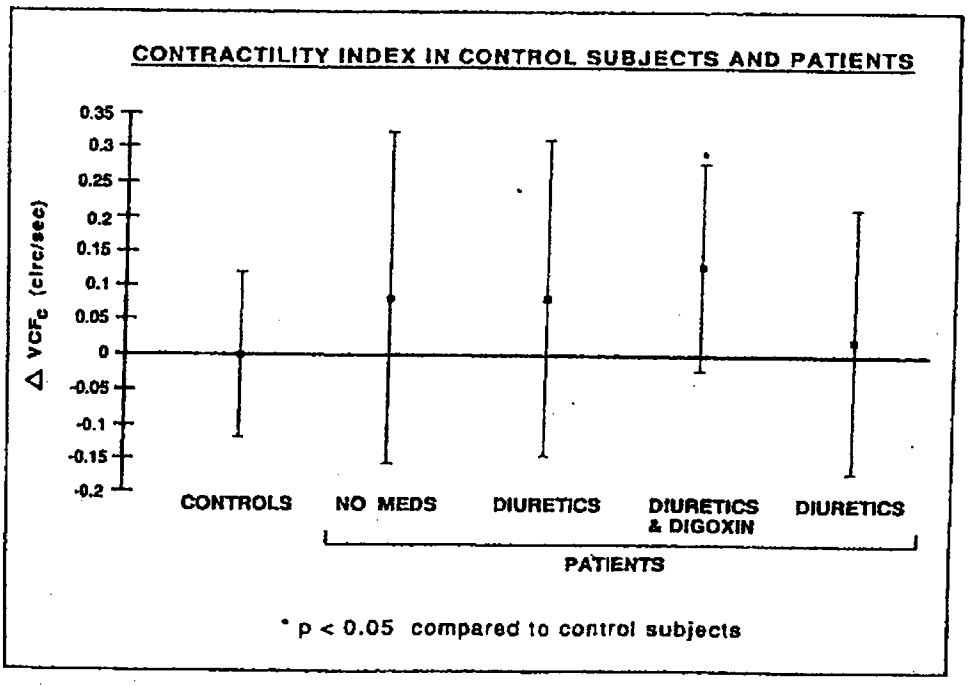
1) Before any meds (baseline)
2) After beginning oral diuretics (evaluation occurred 2.8 weeks after start of therapy)
3) After beginning oral digoxin (evaluation occurred 2.8 weeks after start of therapy)
4) After oral digoxin stopped but diuretics continued (occurred 4.2 weeks after start of therapy).

Drug dose: Oral digoxin 10 μg/kg/day (? Unclear if patient received digitalization/loading dose)

Endpoint measurements: Serum digoxin level, ECG assessments, contractility assessments, clinical assessments.

Results: The mean serum digoxin concentration after being on maintenance therapy was 1.3 ± 0.4 ng/mL.

Figure 5: Contractility Index in control subjects and patients. Data are expressed as mean ± SD . ΔVCF_c = difference between predicted and measured heart rate corrected velocity of circumferential fiber shortening for measured LV end-systolic wall stress.



The authors report that the addition of digoxin to diuretics significantly improved the contractility index relative to the control group (as shown in the figure above). However, as seen in the figure above, the baseline ΔVcF_c was greater in patients than controls. Therefore, the statistically significant difference between patients and controls is of questionable clinical significance.

The authors report that diuretics ± digoxin did not improve symptoms significantly. There were no improvements in weight, respiratory rate or heart rate.

Study title: "Effect of digoxin on left ventricular contractility in newborns and infants estimated by echocardiography" [17]

Population: Newborns (n = 8) and infants (n = 8) in congestive heart failure. All the children had some form of congenital heart disease (e.g. PDA, ASD, VSD, Coarctation, BWG). The newborns ranged in age from 1 to 34 days, and ranged in weight from 1.1 kg to 6.3 kg. The infants ranged in age from 1 to 10 months and ranged in weight from 3.2 to 10 kg.

There were 2 study groups: Group 1 and Group 2. Group 1 comprised the 16 children described above. Group 2 consisted of 11 of the children from Group 1 and 1 additional newborn.

Design: Prospective, non-randomized, unblinded, no control group (all patients served as their own control – baseline control).

Group 1 was studied between 2 and 4 hours after the first digoxin dose. Group 2 was studied after "full digitalization." (? Unclear if this meant steady state was achieved or whether echocardiographic assessment was made after the loading dose was complete).

During the study period, no diuretics or cardioactive drugs other than digoxin were given, nor was fluid intake altered.

Drug Dose: Digitalizing dose (DD) for newborns: 34 μg/kg po or 28 μg/kg IV

Digitalizing dose (DD) for infants: 7 – 8 μg/kg po (1/2 of this dose given as 1st dose, followed by ¼ each after 8 and 16 hours respectively)

Daily maintenance dose = ¼ of DD divided into 2 equal doses.

Endpoint Assessments: Plasma digoxin levels were obtained in blood 8 to 12 hours after last digoxin dose in Group 2.

Echocardiograms were used to measure: left ventricular end-diastolic diameter, left ventricular end-systolic diameter, left ventricular pre-ejection period, and left ventricular ejection period.

Results:

Mean plasma digoxin concentration in Group 2 (chronic dosing group) was = 2.36 ng/mL (range 0.7 to 4.4)

Figure 6: Change of mean V_{cf} and SF before (a) and after (b) the first digoxin dose. (• = newborns, o = infants). V_{cf} = mean circumferential fiber shortening, SF = shortening fraction.

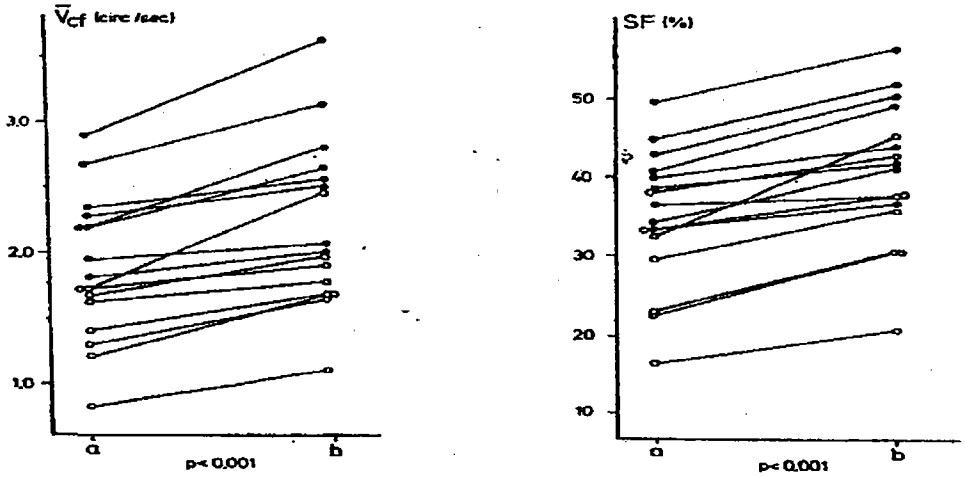
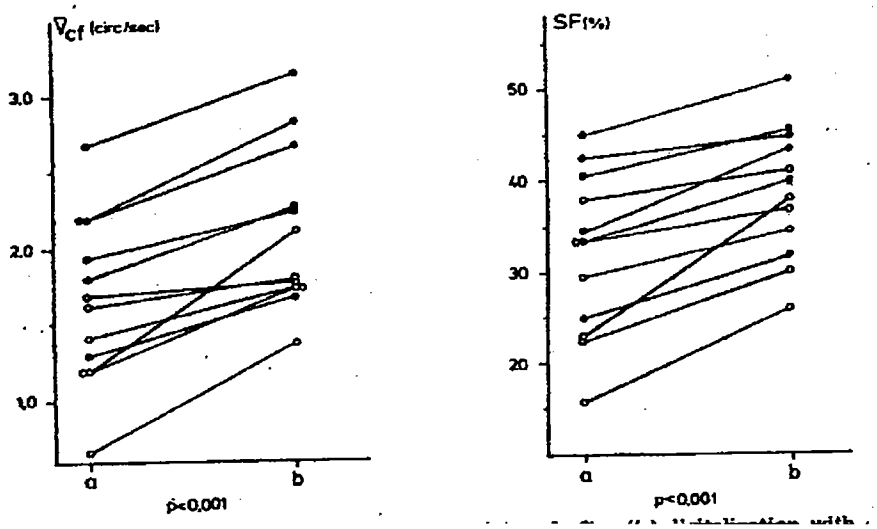


Figure 7: Change of mean V_{cf} and SF before (a) and after (b) digitalization (presumably steady state?) with digoxin dose. (• = newborns, o = infants). V_{cf} = mean circumferential fiber shortening.



As seen in Figures 6 and 7 above there was clear improvement in both groups with respect to shortening fraction and mean velocity of fiber shortening after both the first dose and after "digitalization". The limitations of this study were lack of a placebo group and unblinded echocardiographic assessments. It is unclear whether the echocardiographic findings were associated with symptomatic improvement or not.

Study title: "The use of digitalis in infants and children: a clinical study of patients in congestive heart failure"[18]

Population: 41 consecutive children in symptomatic CHF due to congenital heart disease, myocardial disease, arrhythmia, or rheumatic heart disease. All patients showed clinical evidence of right-sided CHF and at least ½ of patients also had left-sided CHF. Patients ranged in age from 1 month to 14 years.

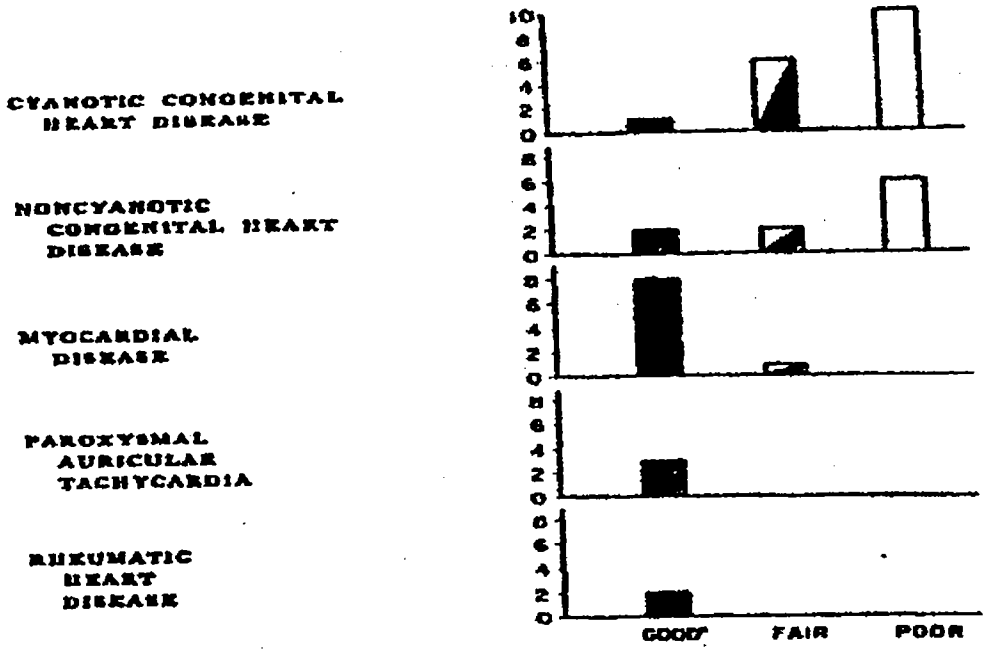
Design: Prospective, non-randomized, unblinded, no placebo control group. Patients evaluated clinically before and after digitalis administration. All children had daily clinical observations and frequent electrocardiographic tracings obtained in close temporal relation to the administration of a cardiac glycoside. The clinical response was termed "good" when all signs of congestion disappeared. The response was considered "fair" if there was noticeable improvement in the evidence of CHF without complete resolution. A "poor" response was one in which no clear-cut evidence of improvement was obtained with therapy.

Drug Dose: 2 preparations of digitalis glycoside were used exclusively in this study. For initial digitalization, the majority of patients received digitoxin IV or by mouth. A few patients received lanatoside C IV. For maintenance therapy, digitoxin was used exclusively. Total digitalizing dose was administered over 24 to 36 hour period in 3 to 4 divided doses. Doses used were 0.01 to 0.05 mg/lb.

Endpoints: Clinical response judged as "good", "fair", or "poor" based on clinical signs and symptoms. For the 3 figures that follow, it is unclear from the manuscript whether clinical assessments were made at steady state in each patient.

Results:

Figure 8: Clinical response to digoxin as a function of diagnosis.



As seen in Figure 8 above, patients with congenital heart disease responded relatively poorly to digoxin. Patients with myocardial disease, paroxysmal atrial tachycardia, and rheumatic heart disease responded relatively well but the number of patients in each case was too small to make any firm conclusions. In addition the absence of a placebo group makes interpretation of this study difficult.

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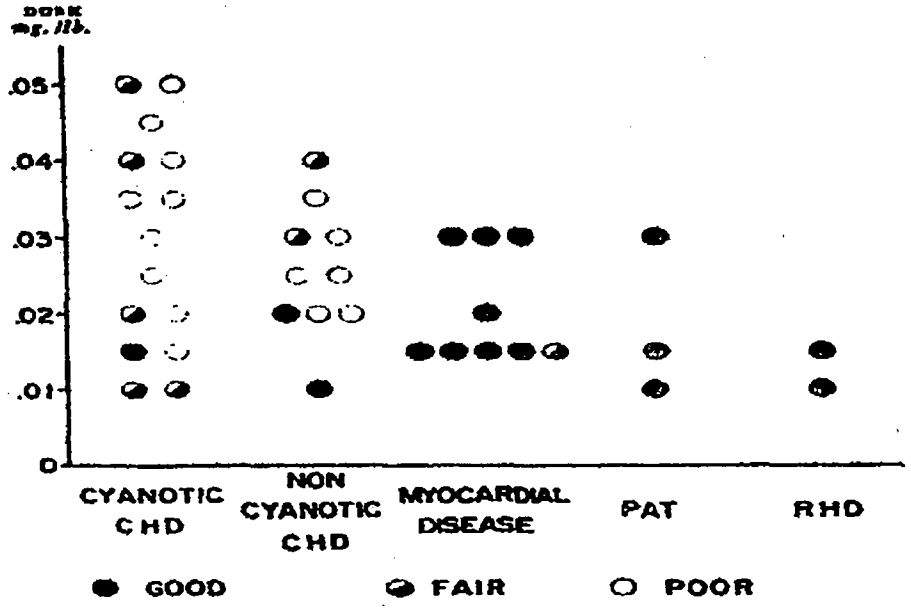
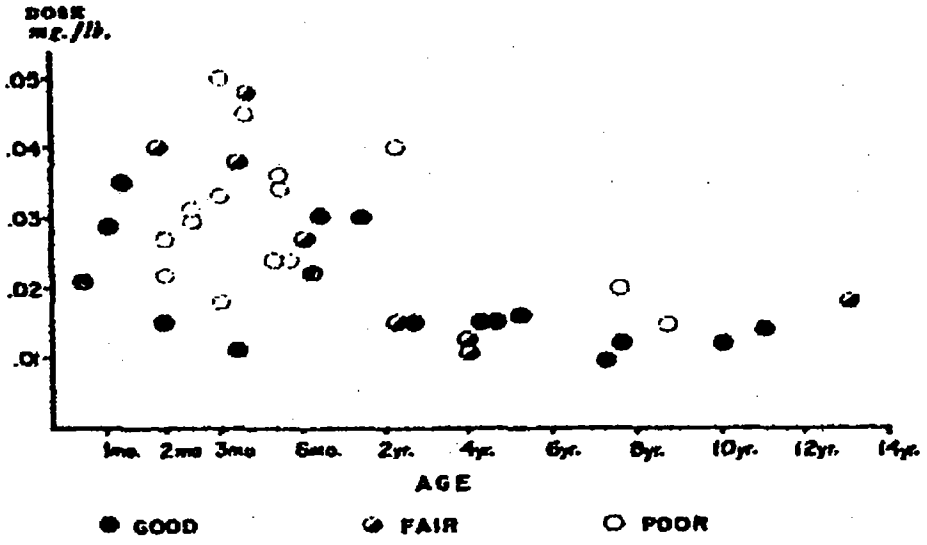
Figure 9: Digitalizing dose (mg/lb) and clinical response.



As seen in Figure 9 above, when doses were effective they tended to range between 0.01 mg/lb to 0.03 mg/lb.

Figure 10: Digitalizing dose (mg/lb) in relation to clinical response and age.



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16/41 enrolled had "good" response. 8/41 had a "fair" response. 15/41 had a "poor" response. 2/41 are unaccounted for. It is unclear when clinical assessments were performed relative to digoxin administration (e.g. it is unclear if steady state was achieved or not). No patient showed a satisfactory response with a dose less than 10 μg/lb. There were no "good responses" occurring at a dose of more than 30 μg/lb. Patients under 2 years of age in general required a slightly higher dose to achieve response compared to a group of children older than 2 years of age.

Study title: "Noninvasive assessment of left ventricular function related to serum digoxin levels in neonates"[19]

Population: 18 neonates, all under 1 month of age and in cardiac failure were included. Patients had congenital heart disease in the form of VSD, PDA, Aortic coarctation, or a right coronary artery to right atrial fistula. Group 1 ("low" serum digoxin level) had a mean age and weight of 18.5 days and 2.25 kg. Group 2 ("high" serum digoxin level) mean age and weight were 9.5 days and 2.1 kg.

Design: Prospective, non-randomized, no placebo control, unblinded study. All 18 neonates received digoxin according to the dosing schedule below. After 5 days of digoxin administration, patients were divided into 2 groups based on serum digoxin levels acquired 6 to 8 hours after last dose : Group 1 had a serum digoxin level < 2.5 ng/mL, Group 2 patients were selected on the basis of a serum digoxin level > 2.5 ng/mL. The use of concomitant drugs (e.g. diuretics) was permitted.

Drug Dose: Loading dose of 18 to 60 μg/kg for the first 24 hours followed by a maintenance dose of 4 to 20 μg/kg qd in 2 divided doses.,

Endpoint assessments: Serum digoxin levels, echocardiography at baseline and post digoxin therapy, and clinical observations. Echocardiographic assessments included measurements of the pre-ejection period (PEP), left ventricular ejection time (LVET), and electromechanical systole (QS_2).

Results: The mean digoxin serum concentration in were 1.99 and 3.62 in Group 1 and Group 2 respectively. There were reductions in PEP, LVET, and QS_2 after 5 days of digoxin therapy among both Groups. There were similar degrees of clinical improvement in both groups as evidenced by a decreased heart rate, regression of hepatomegaly and auscultation.

Study title: "Effects of digoxin in infants with congested circulatory state due to a ventricular septal defect"[20]

Population: 21 neonates, mean age 2.7 months and a mean weight of 3.8 kg. All patients had VSD.

Design: Prospective, non-randomized, no placebo control, unblinded study. No other medications such as diuretics, oxygen, blood transfusion, and fluid/salt restriction permitted.

Drug dose: digitalizing dose ½ of 40 μg/kg IV after which PK collected and from there half-life and volume of distribution calculated. Maintenance dose administered to keep digoxin concentrations at 1.5 ng/mL.

Endpoint assessments: Echocardiographic measurements, determination of Na/K ATPase enzyme activity, clinical assessments (heart size on chest x-ray, heart rate, respiratory rate, diaphoresis, vigor of feeding, weight gain).

Results: 6/21 with echocardiographic improvement. 12/21 patients with clinical improvement (includes the 6 with echocardiographic improvement). There was no statistically significant difference in serum digoxin concentration in the echocardiographic responders (1.7 ng/mL) versus non-responders (1.5 ng/mL).

Study title: "Further evidence suggesting a limited role of digitalis in infants with circulatory congestion secondary to large ventricular septal defect"[21]

Population: 41 infants with large VSD's in "circulatory congestion" and were surgical repair candidates. The mean age was 6 months and mean weight was 5.5 kg.

Design: Prospective, non-randomized, uncontrolled, unblinded.

Drug Dose: 0.01 mg/kg IV

Endpoint assessments: Cardiac catheterization to collect hemodynamic data. Digoxin serum concentrations not measured in this study.

Results: Mean heart rate among the patients decreased by 9 beats per minute on digoxin. Pulmonary artery pressure decreased in patients with lower baseline systemic vascular resistance. Systemic vascular resistance did not improve with digitalis.

Study title: "Digoxin therapy and left ventricular performance in premature infants with patent ductus arteriosus"[22]

Population: 16 premature infants with symptomatic PDA, median gestational age at birth = 29 weeks, median weight = 1.2 kg, 13/16 infants were on ventilator support secondary to hyaline membrane disease.

Design: Digoxin was added to ongoing therapy with diuretics and mechanical ventilation.

Drug dose: Initial dose = 10 μg/kg followed by 5 μg/kg 8 and 16 hours later.

Maintenance dose was 2.5 μg/kg every 12 hours starting 24 hours after initial loading dose.

Endpoint assessments: Serum digoxin levels, Left ventricular systolic time interval, systemic blood pressure. All assessments made 8 to 12 hours after preceding digoxin dose.

Results: LV ejection time was significantly shorter 3 to 7 days after onset of digoxin therapy. The pre-ejection period and isovolumic contraction time was not influenced by digitalization. Clinical effects were judged equivocal with little or no improvement in cardiorespiratory status.

Arrhythmia

Study title: "Re-entrant supraventricular tachycardia in infancy: current role of prophylactic digoxin treatment"[23]

Population: Total of 26 newborns and infants were included; Median age at first presentation was 7 days. 8/26 had structural heart disease. The mechanism of supraventricular tachycardia was pre-excitation syndrome in 9 patients and a concealed accessory atrioventricular pathway in the remaining 17. All patients were symptomatic during their run of SVT.

Design: Retrospective study during a 10 year period ending in 1995.

Drug dose: According to the severity of symptoms, treatment with digoxin was started initially with either IV (n = 16) or oral (n = 10) loading, which was given in 3 or 4 doses and was completed within 24-48 hours. Oral dosage for chronic treatment was 0.015 mg/kg/day in 2 daily doses for infants less than 10 kg.

Endpoint assessments: Recurrence of SVT after completion of IV or oral digoxin loading. Failure of digoxin was defined as the need for alternative medical intervention to terminate further episodes of SVT

Results: During the 10 year study period 48 neonates and infants were seen for paroxysmal SVT. In 5 of these cases the underlying arrhythmia was atrial flutter and therefore these children were excluded. In 6 of the 48, SVT terminated spontaneously. In 6 additional patients had documented SVT but did not receive treatment with digoxin. There were 3 patients with documented SVT and who received digoxin that were excluded because recent follow-up data could not be obtained.

The results of the study are summarized in the Table 5 below. The mean duration of digoxin therapy was 12 months (range 4 months to 18 months). The mean serum digoxin levels in patients achieving complete or partial "success" was 1.74 ng/mL while in the "failure" patients it was 2.0 ng/mL.

Table 5: The effect of digoxin therapy on SVT in 26 neonates and infants[a].

Tachycardia mechanism	# of patients	Response to digoxin		
		Success	Partial effect	Failure
Pre-excitation	9	5	1	3
Concealed pathway	17	12	1	4
Total	26	17	2	7

[a] The results in this table represent outcomes during the mean 12 month duration of digoxin therapy. After this mean 12 month digoxin therapy period was complete subjects were withdrawn from digoxin. After withdrawal 16 experienced no further arrhythmias while 1 experienced recurrent attacks starting 6 months post withdrawal. The 2 patients with "partial effect" experienced no further SVT attacks during the withdrawal period.

Limitations of study: This was a retrospective study. It is unclear how many of the "successes" were due to spontaneous conversion to sinus rhythm versus digoxin drug effect. It is important to note that among the 48 patients reviewed for entry into this retrospective study, 6 of them reverted to sinus rhythm spontaneously. Lack of a control group makes interpretation of a study such as this difficult.

Study title: "Supraventricular tachycardia in children: clinical features, response to treatment, and long-term follow-up in 217 patients"[24]

Population: 217 children with first episodes of SVT before the age of 18 years (median age = 24 months). 60% with normal hearts, 23 % with congenital heart disease, symptomatic CHF in 24%. Patients with atrial fibrillation or flutter were

excluded. Of note the 217 patients collected in this study were acquired from approximately 17,700 patients referred to the Section of Pediatric Cardiology at Texas Children's Hospital over a 25 year period.

Design: Retrospective

Drug Dose: Initial treatment with IV digoxin as a digitalizing dose = 40 to 50 μg total. Digoxin maintenance dose was 10 μg/kg/day (formulation and manufacturer not specified).

Endpoint assessment: Successful treatment/response for initial therapy was considered as cessation of SVT for at least one hour. After maintenance therapy with digoxin, recurrence was defined as SVT reappearance after at least 7 days freedom from the dysrhythmia.
Results: IV digoxin (loading dose) was "successful" as defined above in 68% of all patients, in 96% of patients with WPW, and in 59% of patients without pre-excitation. With chronic (maintenance) dosing, only 17% had a sustained resolution of their SVT.

It is important to note that 28% of patients had resolution of SVT before any treatment was initiated.

Limitations of study: Retrospective study; The definition of response after IV dosing did not include a statement of sustained cessation of dysrhythmia; Although recurrence rates after maintenance therapy with digoxin were evaluated, these were confounded by the fact that subjects were allowed to receive treatment with propranolol or quinidine.

Study title: "Wolff-Parkinson-White syndrome and supraventricular tachycardia during infancy: management and follow-up"[25]

Population: 90 children with WPW/SVT with initial onset in the first 4 months of life (mean age at presentation = 29 days). 63% of patients were male; structural heart disease was present in 20%; Congestive heart failure was present in 54%; None of patients had atrial fibrillation or flutter. Mean follow-up period was 6.5 years.

Design: Retrospective study; The 90 patients in this study were collected over a 31 year period.

Drug Dose: Neither the formulation of digoxin used nor the specific doses used are discussed in the manuscript.

Endpoint assessment: Recurrent arrhythmia

Results:

Table 6 below summarizes the results of treatment of the initial episode SVT.

Table 6: Results of conversion to normal sinus rhythm during initial episode of SVT

	# of patients (%)
Spontaneous conversion	8(9)
Digoxin administration	58 (65)
Electrical cardioversion	13 (14)
Other[a]	11 (12)
Total	90 (100)

[a] Includes administration of multiple drugs, vagal maneuvers, ice to forehead, verapamil, methoxamine

Recurrent SVT: 37/90(41%) experienced SVT as a single episode or as brief recurring episodes only during their initial hospitalization. 30/90 (33%) had recurrent SVT after 1 year of age and all 30 of these patients continued to have recurrences beyond 18 months of age.

60 patients that were followed up for more than 2 years. Of these 25 (42%) continued to have episodes of tachycardia.

For maintenance, digoxin was the only medication used in 55 (61%) patients; 33 (37%) patients required additional therapy to control SVT;

Study limitations: Similar to the other retrospective studies, not having a control group makes it difficult to interpret the study findings. However, it is clear from this and other studies that some patients spontaneously convert to sinus rhythm in the absence of any drug therapy. Therefore, without a control group, it is difficult to assess the true effectiveness of digoxin.

Study title: "Atrial flutter in the young: a collaborative study of 380 cases"[26]

Population: N = 380 children with electrocardiographically documented atrial flutter with age of onset between 1 to 25 years (mean age of onset = 10.3 years). 60% of these children had repaired congenital heart disease, 13% had palliated congenital heart disease, 8% had un-operated congenital heart disease, and 8% had "normal" hearts, 6% had cardiomyopathy, 4% had rheumatic heart disease, and 2% had other lesions. 75% of the patients described here had at least 1

operation at a mean age of 5.2 years. In the majority of these patients, atrial flutter developed 1 to 5 years post surgery.

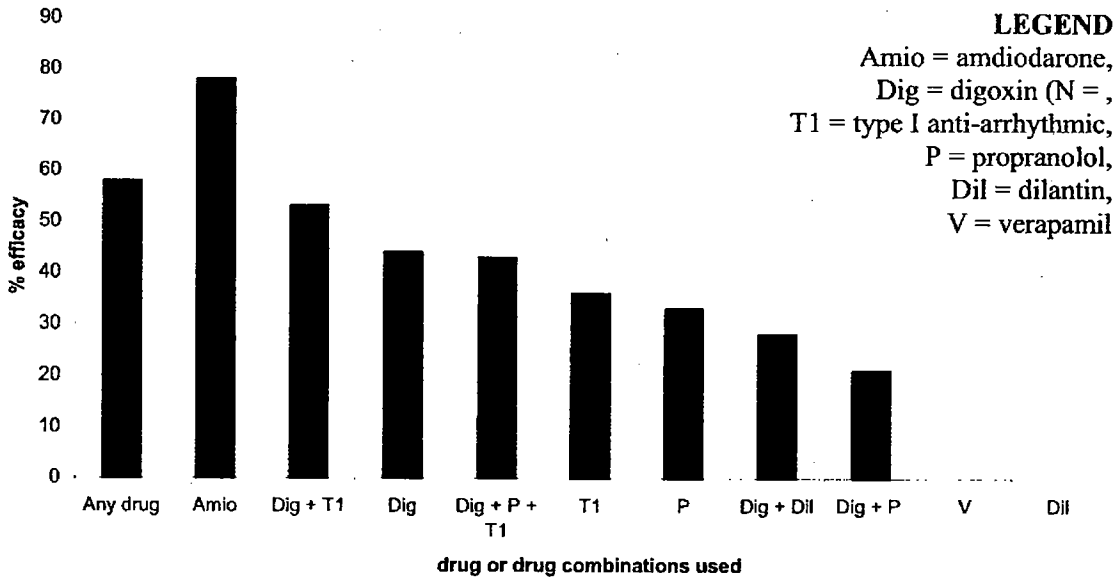
Design: Retrospective data collection

Drug dose: Neither dose nor formulation stated in this manuscript. There is no comment on the duration of therapy.

Endpoint assessments: "Response" was defined as an abolition of episodes of atrial flutter for at least 1 year and continued absence throughout the duration of follow-up by clinical history, routine ECG monitoring, or ambulatory ECG monitoring.

Results:

Figure 11: Long term drug efficacy in 347 patients



[a] Any drug (N = 347), Amio (N = 9), Dig + T1 (N = 105), Dig (N = 235), Dig + P + T1 (N = 14), T1 (N = 25), P (N = 18), Dig + Dil (N = 7), Dig + P (N = 56), V (N = 2), Dil (N = 1).

Follow-up was done for 357 of the 380 patients; 297 (83%) were alive at an average follow-up time of 6.5 years (range 1 month to 22.3 years). 60 patients (17%) had died an average of 2.4 years after the first episode of atrial flutter.

Study limitations: Retrospective study. No conclusions can be made of the true efficacy of digoxin without a control group.

Study title: "Paroxysmal supraventricular tachycardia in infancy and childhood"[27]

Population: 39 cases of SVT presenting in infancy were studied. Generally the first attack occurred during the 1st 12 months of life. At least one attack had to be documented electrocardiographically. 3/39 children had congenital heart disease. Symptoms of cardiac failure were present in all patients in whom tachycardia persisted for > 24 hours (Unclear how many subjects were in this category).

Design: Retrospective data collection

Drug dose: Neither dose nor formulation was well documented in this manuscript.

Endpoint assessments: Termination of tachycardia.

Results: The results are divided by the type of SVT noted in each patient.

Paroxysmal SVT of unknown origin (N = 8)

All 8 treated with digoxin: DD = 60 to 80 μg/kg over 24 hours, MD = 15 to 20 μg/kg/day. 7/8 were restored to Normal sinus rhythm promptly. It is unclear if this response was sustained in any of the subjects).

Atrial fibrillation (N = 1)

Treatment with digoxin not successful in this one patient (administered dose not stated).

Atrial flutter (N = 8)

6/8 cases treated with digoxin
3/6 treated patients were restored to sinus rhythm
1/3 that was treated and restored to NSR had a recurrence.

AV nodal re-entry tachycardia (N = 8)

Digoxin effective in terminating tachycardia in 8/8 subjects
5/8 had recurrences of tachycardia despite digoxin prophylaxis ± inderal and quinidine.

WPW (N = 16)

All these patients were treated with digoxin
12/16 reacted with conversion to NSR
5/12 that converted to NSR had occasional short, early recurrences

2/12 that converted to NSR had multiple, severe recurrences

Study limitations: Doses not reported for all patients; This was a retrospective study; Lack of a control group;

Study title: "Atrial automatic tachycardia in children"[28]

Population: 9 children with atrial automatic tachycardia, age of onset between pre-natal and 14.3 years (median 6.6 years). These 9 patients were studied from January 1980 to January 1987. The diagnosis was made electrocardiographically and electrophysiologically. 8/9 subjects had presenting symptoms of congestive heart failure while 1/9 had symptoms of pre-syncope.

Design: Retrospective

Drug dose: Drug therapy was started with digoxin and progressed through beta-blocking agents, quinidine, verapamil, amiodarone, ethmozine, or propafenone. Drugs were increased to maximum allowed by safety considerations or until measured serum levels were in target range. Doses of various medications used were not stated.

Endpoint assessments: Control of atrial automatic tachycardia
"Full control" was defined as total abolition of AAT and restoration of sinus rhythm;

"Good control" was defined as persistence of tachycardia but at a reduced rate to the extent that symptoms resolved and cardiac size and function normalized as determined by chest x-ray and echocardiogram;

"Partial control" was defined as reduction of the tachycardia rate to alleviate symptoms, with some symptoms remaining or cardiac size and function remaining abnormal as evidenced by chest x-ray and echocardiogram

"Ineffective" was defined as neither restoration of sinus rhythm nor meaningful reduction in heart rate or symptoms.

Results:

Table 7: Medical treatment of 9 children with atrial automatic tachycardia with various anti-arrhythmic therapy.

Drug	# of trials	"Full control"	"Good control"	"Partial control"	"Ineffective"
Digoxin (Dig)	9			3	6
Dig + Propranolol	4				4
Dig + Metoprolol	2			2	
Dig + Quinidine	3			1	2
Dig + Verapamil	2				2
Verapamil	5	1			4
Sotalol	4	1	1	1	1
Amiodarone	2	1			1
Ethmozine	1				1
Propafenone	1	1			
Total	33	4	1	7	21

Study Limitations: It is unclear if the definition of "full control" referred to a sustained response or not. The doses of the various anti-arrhythmics used were not reported. This was a retrospective study. No control group was present.

Study title: "Atrial flutter in the human fetus: diagnosis, hemodynamic consequences, and therapy"[29]

Population: fetuses; in utero treated with digoxin

Design: Retrospective

Drug dose: Digoxin administered transmaternally; Given IV for 2 days followed by 0.25 mg per OS.

Endpoint: Reversion to normal sinus rhythm.

Results: Over 7000 in utero, fetal echocardiographic examinations were performed at a University Hospital in Belgium. From this group, 10 fetuses were found to have atrial flutter.

8/10 fetuses with atrial flutter were treated with Digoxin transmaternally. Treatment was successful in 5 of the 8 treated patients. Treatment unsuccessful in 3 of the 8 treated patients. **One of treatment failures died with subsequent autopsy revealing an accessory pathway.**

Limitations: It is unclear how "success" was defined (e.g. was the response sustained and for how long). This was a retrospective study. There was no control group.

Study title: "Natural history of isolated atrial flutter in infancy"[30]

Population: Total of 9 patients (3 males, 6 females). Age at onset was pre-natal to 6 weeks after birth. Mean birth weight was 3.3 kg. None with congenital heart disease. Mean heart rate was 397 beats per minute. 6 of these 9 patients had other peri-natal problems (e.g. hydrops, pneumonia, anemia, low birth weight, etc.)

Atrial flutter was identified by the typical saw tooth pattern on a surface ECG.

Design: Retrospective

Drug dose: Not stated in manuscript

Endpoint: Reversion to normal sinus rhythm

Results: 2/9 subjects with spontaneous reversion to sinus rhythm (occurred within 22 to 24 hours).
4/9 subjects reverted to sinus rhythm with overdrive pacing (conversion occurred instantaneously).
3/9 subjects reverted to sinus rhythm with oral digoxin - dose unknown. (conversion occurred within 11.5 to 28 hours post drug administration).

Study Limitations: It is unclear if the response was sustained and if so for how long. There were subjects who converted spontaneously to sinus rhythm. It is therefore difficult to judge the true efficacy of digoxin without a control group.

D. Efficacy Conclusions

The quality of pediatric studies from the literature do not provide conclusive evidence of efficacy based on standards used by the Food and Drug Administration today. The majority of the studies in literature are uncontrolled, unblinded studies or retrospective studies from which limited conclusions on the efficacy of digoxin can be made. In some of the studies, the endpoints evaluated are not clinically meaningful.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The most well described form of digoxin toxicity in pediatric populations is cardiac toxicity. Some of the types of cardiac toxicity that have been reported include sinus node depression with escape rhythms, atrio-ventricular block, ventricular fibrillation, premature ventricular contractions, nodal tachycardias, severe bradycardia, and paroxysmal atrial tachycardia. Non-cardiac forms of toxicity have been reported but with much less frequency. The evaluation of non-cardiac forms of toxicity can be difficult especially among neonates and infants that have not developed skills to verbalize complaints. Examples of non-cardiac toxicity that have been reported include vomiting and poor feeding.

When digoxin toxicity has been identified in a patient, a corresponding blood level has not always been obtained. This makes it difficult to adequately characterize the relationship between digoxin serum concentrations and toxicity. In instances where toxicity has been identified and digoxin concentrations have been measured, the digoxin concentrations were greater than 2 ng/mL. One prospective, dose tolerability study done in premature neonates suggests a clear, dose-dependent relationship between digoxin concentrations and toxicity[31]. Cardiac toxicity was the main form of toxicity described in this study.

B. Description of Patient Exposure

Obtaining an accurate assessment of patient exposure is difficult because not all the reported studies specify the duration of therapy. Patient exposure can be roughly estimated at best. For several of the studies listed in the Table 8 below, the duration of exposure was relatively short (e.g. 1 day and 1 week). One of the retrospective studies cited below noted patient exposure on digoxin being between 1 day and 1 year.

C. Methods and Specific Findings of Safety Review

Table 8 below is a summary of several studies in which digoxin toxicity was described. Many of the studies listed in this table did not have as their primary endpoint, a characterization of digoxin toxicity in pediatric patients. Often times digoxin toxicity was reported secondarily.

Table 8: Summary of studies describing digoxin toxicity in pediatric populations

Reference	Patient demographic	Frequency of dig. Toxicity	Serum digoxin Concentration	Description of toxicity
Nadas 1953[a, 18]	Children in symptomatic CHF due to congenital heart disease, myocardial disease, arrhythmia or rheumatic heart disease	3/41 had vomiting. 11/41 had electrocardiographic evidence of toxicity.	Not measured	Vomiting occurred in patients with doses greater than 0.03 mg/lb. Electrocardiographic abnormalities occurred at doses ranging from 0.015 to 0.03 mg/lb.
Levine 1962[b, 31]	Healthy premature infants	12/80 had electrocardiographic evidence of toxicity	Not measured	See description in reference below.
Levine 1962[b, 32]	Healthy Premature infants and one term neonate administered digoxin within one month of birth.	Not applicable in this retrospective study.	Not measured	Sinus node depression with suprventricular escape rhythm (n = 7), AV block (n = 4), ventricular premature contractions (n = 1), intraventricular conduction delay with widened QRS (n = 1), ventricular fibrillation (n = 1).

Table 8 cont'd				
Larese 1974[33]	Pediatric patients ranging in age from 7 days to 12 years. All had congestive heart failure associated with congenital cardiac malformation.	4/15 patients had electrocardiographic abnormalities compatible with digoxin intoxication.	Digoxin level for subject with 2° AV block = 3.6 to 3.9 ng/mL on the 10th day of digoxin therapy 4 to 6 hours after maintenance dose. Digoxin level for subject with pre-mature ventricular contractions = 4.0 ng/mL 5 hours after maintenance dose. Digoxin level = 3.8 to 5.0 ng/mL 4 to 6 hours after maintenance dose. Digoxin level = 2.3 to 2.5, 3 to 5 hours after maintenance dose.	2° AV block Pre-mature ventricular contractions "Nodal tachycardia"
Krasula 1974[b, 34]	Infants and children n = 16 toxic n = 75 non-toxic	Not applicable in this retrospective study	See Figure 12 below	AV block (1st and 2nd degree), VPB's; atrial flutter, atrial tachycardia with block, AV dissociation; Vomiting that ceased after discontinuation or decrease in dosage (6 of the 16 toxic patients had vomiting).
Hayes 1973[b, 35]	Infants (1 week to 11 months of age) Children (2 to 14 years of age)	Not applicable in this retrospective study. There were 5 toxic and 31 non-toxic infants There were 10 toxic and 33 non-toxic children.	See Figure 13 below. Mean serum digoxin conc. In toxic infants and children were 4.4 and 3.4 ng/mL respectively; Mean serum digoxin concentrations in non-toxic infants and children were 2.8 and 1.3 ng/mL respectively.	Arrhythmias compatible with digitalis toxicity and in whom the rhythm reverted to normal after digoxin administration.

Table 8 cont'd				
Neutze 1977[36]	Group 1: Infants and neonates ages ranging from less than 1 month to 18 months. (n = 53) Group 2: Infants, neonates, and children ages ranging from less than 1 month to 17 years. (n = 44)	1/53 in Group 1 developed signs of clinical toxicity The serum digoxin level was 4.3 ng/mL in this patient 1/44 in Group 2 developed evidence of clinical toxicity.	Serum digoxin level in the toxic infant in Group 1 was 4.3 ng/mL while the mean level in non-toxic infants of similar age was 1.4 ng/mL. Serum digoxin level in the toxic neonate in Group 2 was 6.1 ng/mL while the mean level in non-toxic infants of similar age was 2.8 ng/mL. (Patients received digoxin for at least one week prior to blood sampling. Blood specimen was obtained 7 to 12 hours after the last dose of digoxin.)	Poor feeding and 2nd degree AV block in an infant in group 1. Frequent ventricular premature beats in an infant in Group 2.
Berman 1978[37]	Low birth weight infants with PDA	9/30 in retrospective study 5/16 in prospective study	4.8 to 13.0 ng/mL Avg. = 5.4 ng/mL	Primarily electrocardiographic (e.g. AVB, episodic severe bradycardia, death, PR prolongation)
Halkin 1978[b, 38]	Infants and neonates aged 1 week to 2 years (mean = 21 weeks)	4/34 were toxic (Of the toxic patients all 4 had digoxin levels greater than 2 ng/mL while 9/30 that were non-toxic had levels greater than 2)	2 to 4.6 ng/mL (important to note in this study that digoxin levels were drawn after at least 3 days of digoxin therapy, 8 hours after dose administration.)	Primarily electrocardiographic (e.g. PVC's, AV escape rhythm, AV dissociation, Heart block, PAT with block, sinoatrial exit block).

Table 8 cont'd				
Pinsky 1979[b, 39]	Premature Neonates with signs of PDA/Cardiomegaly /hepatomegaly (n = 37)	1/37 developed evidence of toxic cardiac effects.	Digoxin level = 5.1 ng/mL (Digoxin serum level measured after receiving a minimum of 4 maintenance doses. The blood sample was drawn 12 hours after a maintenance dose).	Atrioventricular block (2:1)

[a] Please refer to efficacy section of review for more study details of this study by Nadas et. al.; In this study, digitalis, a glycoside related to digoxin was used.
[b] Detailed description of these studies follow this table.

The evaluation of drug induced toxicity can be difficult in a pediatric population, particularly among neonates and infants who have not yet developed skills to vocalize complaints. Often times, objective measures are relied upon to assess drug induced toxicity. As can be seen from Table 8 above, electrocardiographic toxicity was the most common form of toxicity. In certain instances the toxicity was benign in nature (e.g. PR prolongation) while in other instances it was more severe (e.g. ventricular fibrillation). Non-electrocardiographic evidence of toxicity included vomiting and poor feeding. Not every study listed in this table measured plasma digoxin concentrations. Therefore it is difficult to correlate plasma digoxin concentrations with toxicity. When toxicity did occur in a patient and the digoxin concentration was measured, it was generally greater than 2 ng/mL. It is very difficult to provide an accurate assessment of the contribution of digoxin to toxicity in pediatric patients from the available data because many of the listed studies do not have appropriate control groups. A control group is needed because the types of patients to which digoxin was administered (e.g. patients in congestive heart failure secondary to congenital heart disease) may be susceptible to various arrhythmias independent of digoxin use. Without a control group, it is difficult to assess to what extent digoxin contributes to toxicity. Recognizing these limitations, the frequency of electrocardiographic toxicity with the use of digoxin in a pediatric population ranges from 5% to 31%. The frequency of vomiting with the use of digoxin ranged from 7% to 38%.

Study title: "The use of digitalis in infants and children: a clinical study of patients in congestive heart failure"[18]

3 of 41 cases with doses greater than 0.03 mg/lb had vomiting. 11 of 41 cases had electrocardiographic evidence of toxicity: ventricular ectopic beats (n = 3), AV block (n = 4), changing pattern of P waves (n = 4). These electrocardiographic abnormalities occurred at doses ranging from 0.015 to 0.03 mg/lb.

Study title: "Digoxin dosage in premature infants"[31]

This study was a prospective, randomized, baseline control study of 80 healthy neonates, weighing between 1,000 and 2,500 grams. All were required to have normal baseline electrocardiograms within 72 hours of digoxin administration. Three digitalizing/test doses of digoxin were administered: 30 μg/kg, 50 μg/kg, and 75 μg/kg. The total daily dose was equally divided in three parts and administered 8 hours apart. Electrocardiograms were acquired after the third dose (Nursing staff was requested to collect electrocardographic data from a direct writing machine prior to the 3rd dose). The diagnosis of digitalis toxicity was made solely on the basis of electrocardiographic criteria. It was necessary for electrocardiographic evidence of toxicity to appear during or shortly after the 3 doses were completed and that there be evidence of resolution of the electrocardiographic toxicity in subsequent tracings. Electrocardiographic toxicity was defined as "higher grades of block, as well as any ectopic beats or rhythms were accepted as a reflection of over dosage. Sinus arrhythmia, sinus bradycardia, and changes in ST-T configuration were considered to be manifestations of digitalis effect rather than intoxication.

Table 9: Results of a prospective, randomized study, baseline control study evaluating the frequency of digoxin IM electrocardiographic toxicity in healthy premature neonates.

Digitalizing dose (μg/kg)	Number tested	Number intoxicated (%)
30	27	0 (0%)
50	26	3 (11.5%)
75	27	9 (33.3%)

Study title: "Digitalis intoxication in premature infants"[32]

The present study was a retrospective analysis of the toxic manifestations of digitalis that occurred in 13 premature but otherwise healthy infants. One additional case was that of a normal full-term newborn infant. The 13 premature neonates were administered digoxin no later than 1 month after birth. Their weights ranged from 1kg to 2.5kg. The one full-term newborn in this analysis received digoxin within 72 hours of birth and weighed more than 2.5kg. All newborns in this analysis received digoxin intramuscularly.

The manifestations of digitalis intoxication noted in this study were primarily electrocardiographic in nature and consisted of sinus node depression with supraventricular escape rhythm (n = 7), atrioventricular block (n = 4), ventricular premature contractions (n = 1), intraventricular conduction delay with widened QRS (n = 1), ventricular fibrillation (n = 1). No plasma digoxin levels were measured in this study.

Three infants were intoxicated by 34 μg/kg in two divided doses 8 hours apart. Three infants were intoxicated by 50 μg/kg in either two or three divided doses (this included the newborn that developed ventricular fibrillation). In the remaining 8 infants toxicity was induced by 75μg/kg given in 3 divided doses at 8 hour intervals.

Note: this study is a supplement of the previous study (reference # 31).

Study title: "Digoxin intoxication in infants and children: correlation with serum levels" [34]

A study by Krasula et. al. evaluated the differences in serum digoxin levels between infants and children classified as digoxin toxic compared to a group of infants and children that were not classified as digoxin toxic.

Population: There were 12 infants and 4 children in the study. The 12 infants ranged in age from 2 days to 5 months while the 4 children ranged in age from 5 to 12 years. All the children had congestive heart failure secondary to congenital cardiac malformations, cardiomyopathy, or cystic fibrosis. The comparator group in this study consisted of 22 non-toxic infants and 53 non-toxic children.

Serum concentrations of sodium, potassium, BUN and hematocrit were within normal limits for age in all patients except one that had mild azotemia, hyperkalemia (6.3 mEq/L), and hyponatremia (129 mEq/L).

Design: Prospective, controlled, non-randomized, partial blinding. Assessment of digoxin toxicity was made investigators blinded to digoxin plasma concentrations.

Doses: DD = 80 μg/kg orally or 45 μg/kg IM over 16 to 24 hours (only subset of digoxin toxic patients got a "digitalizing dose"). Similar doses were given to non-

toxic patients in the control group. Maintenance doses were approximately 20 μg/kg for infants, 15 μg/kg for children 9 to 18 kg, and 10 μg/kg for children over 18 kg in divided doses every 12 hours. Formulation used was Lanoxin elixir (Burroughs Wellcome and Co.)

Endpoint assessments: Serum digoxin concentrations were obtained in patients that were on digoxin for at least one week or longer. Only in the subset of patients that received a digitalizing (loading) dose were the levels measured after loading rather than at steady state.

Results: Manifestations of toxicity included both electrocardiographic changes and clinical signs (e.g. 1st and 2nd degree AV block, PVC's, premature junctional beats, Sinus bradycardia with premature atrial beats, atrial tachycardia with variable block, supraventricular premature beats, AV dissociation, persistent vomiting, and bradycardia during feeding).

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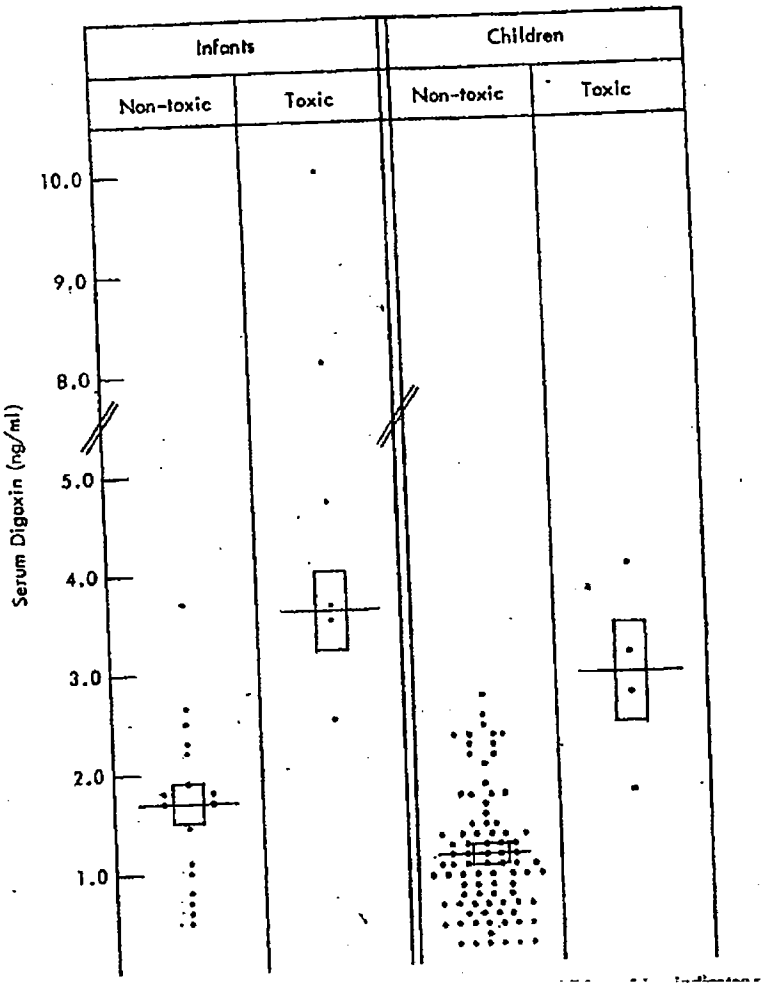
Figure 12 below shows the serum digoxin concentrations at steady state among toxic and non-toxic infants and children.

Figure 12: Serum digoxin concentrations (ng/mL) obtained in infants and children on digoxin for at least one week. Horizontal line indicates mean and bars represent S.E.M.



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The study also states that for subset of children that underwent a loading/digitalization dose, the mean serum digoxin concentrations were equivalent to those of non-intoxicated infants. This supports the notion that plasma concentrations obtained after an initial loading dose may not be as predictive of toxicity as levels obtained at steady state.

Study title: "Serum digoxin studies in infants and children"[35]

This study similar to the study above aimed to compare the plasma digoxin concentrations among toxic and non-toxic children.

Population:

(Control Group – non digoxin toxic patients)

Infants (N = 31) – 1 week to 11 months of age; 30 with congenital heart disease and 1 with SVT.

Children (N = 33) – 2 to 14 years of age; 29 with congenital heart disease, 2 with cardiomyopathy, 1 with chronic rheumatic valvular disease, 1 with acute rheumatic fever.

Adults (N = 24)

(Digoxin toxic patients)

This group of patients was comprised of individuals that manifested arrhythmias compatible with digitalis toxicity and in whom the rhythm reverted to normal after digoxin discontinued. The arrhythmias seen consisted of aberrant supraventricular rhythms with or without block, 2nd degree AV block, multi-focal PVCs, ventricular bigeminy, or ventricular tachycardia.

Infants (N = 5) – 1 week to 11 months of age
Children (N = 10) – 2 to 14 years of age
Adults (N = 4)

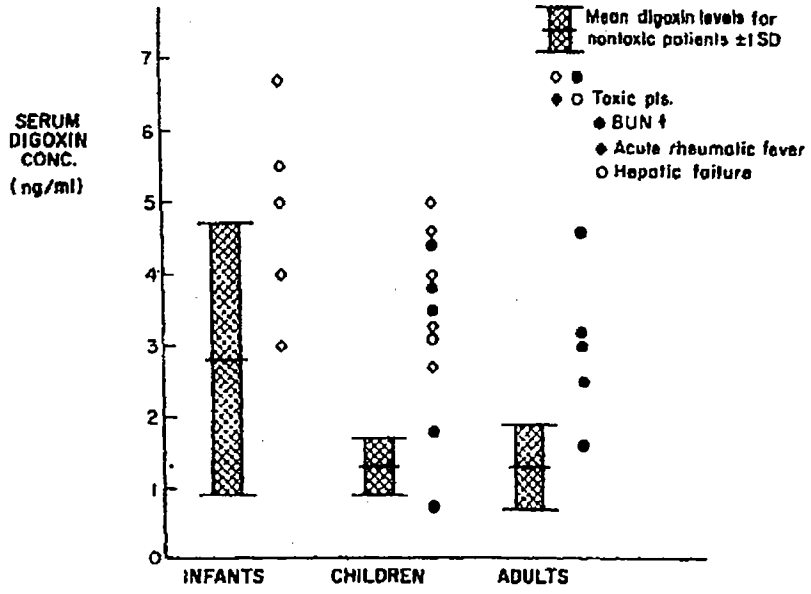
Design: Unclear if this was a prospective or retrospective study; unclear if blinded or not;

Dose: MD in infants ranged from 14 to 28 μg/kg/day. Younger children received 10 to 17 μg/kg/day while older children received 6 to 10 μg/kg/day. Adults received between 1.3 to 11.5 μg/kg/day. Oral preparation of Lanoxin (from Burroughs Wellcome) was used.

Endpoint assessment: Each of the patients had been receiving maintenance digoxin therapy for at least 3 days when serum levels were measured. Plasma samples were obtained 6 to 24 hours after digoxin administration.

Results:

Figure 13: Individual serum digoxin concentrations (ng/mL) measured in toxic infants, children, and adults compared with the levels (± 1 SD) observed in non-toxic patients in each age group.



Limitations of study: Steady state may not been reached among all study patients if waited only 3 days before acquiring digoxin plasma samples. The half-life of digoxin in infants is quite variable and has been reported to be as high as 150 hours.

Study title: "Steady state serum digoxin concentration in relation to digitalis toxicity in neonates and infants"[38]

Digoxin toxicity manifested in the form of multifocal ventricular premature beats (conc = 2.0 ng/mL), atrial fibrillation-flutter and subsequently death (conc = 4 ng/mL), multifocal premature ventricular contractions and AV dissociation and eventually death (conc = > 3), paroxysmal atrial tachycardia with block (conc = 3.7).

Pinsky WW, Jacobsen JR, Gillette PC, Adams J, Monroe L, McNamara DG. Dosage of digoxin in premature infants. J Pediatr. 1979;94:639-42[39].

This study evaluated the serum digoxin concentrations achieved during maintenance therapy in premature infants. Two different doses of digoxin were evaluated. In "Phase I" (N = 25), each patient digitalized with 30 μg/kg given IV: ½ administered immediately then ¼ given 8 to 12 hours after the initial dose; the remaining ¼ given another 8 to 12 hours after initial dose. The maintenance dose was 1/8 of the total dose given every 12 hours. At least 72 hours after digitalization, blood was withdrawn for measurement. There was an inverse correlation between the measured digoxin level and the body weight at birth. However in "Phase II" (N = 12), each patient was digitalized with 20 μg/kg IV in a similar fashion to "Phase I". The maintenance dose was also 1/8 of the total dose given every 12 hours. This dosing regimen produced constant digoxin levels regardless of body weight at birth.

In this study no patient was receiving any other inotropic or chronotropic medication. A subset of patients in each phase had pre- and post-digitalization echocardiograms. Shortening of the LV ejection time and of the pre-ejection period was found after digitalization in each patient. The clinical significance of this echocardiographic endpoint is unclear. Additionally, I am not sure what to make of this finding in the absence of a control group.

In this study 1 of the 37 infants experienced cardiac toxicity in the form of a 2:1 AV block.

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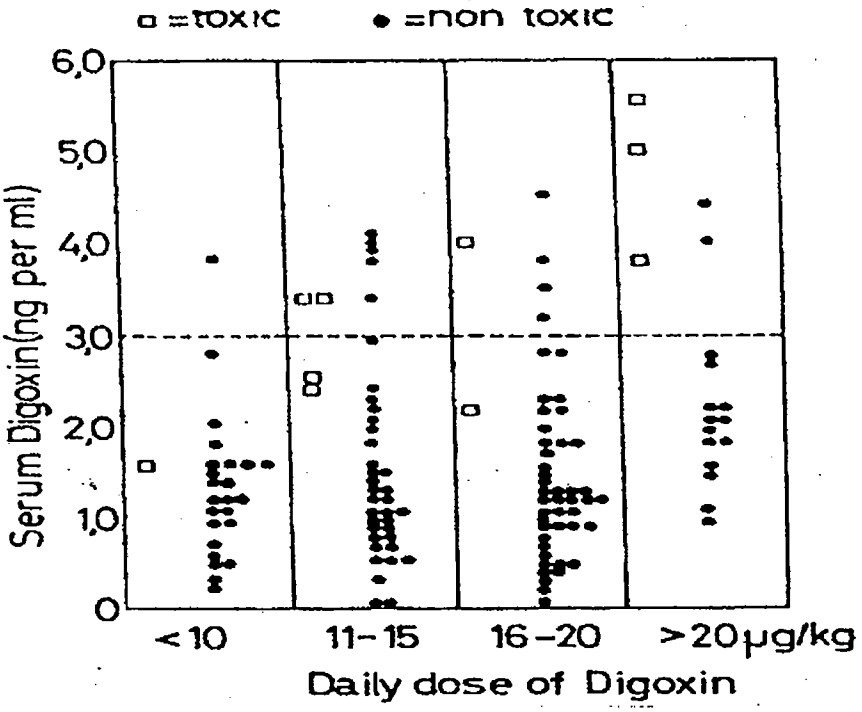
Study title: "Serum digoxin in adults and children"[40]

The figure below shows comparison of the serum digoxin concentrations obtained from 24 non-toxic children aged 5 days to 2.5 years (total of 124 serum samples) and from 4 infants regarded as toxic (total of 10 samples). According to the authors serum samples were acquired at (steady state).

Figure 14: Serum digoxin concentrations (ng/mL) in toxic (□) and non-toxic (•) children.



D. Adequacy of Safety Testing

The safety database for digoxin could be better. The frequency with which arrhythmias occur could be better characterized. Having a placebo arm would help in better characterizing the relative risk of arrhythmia on digoxin relative to placebo because the patient population we are dealing with (congenital heart disease) may potentially be prone to certain arrhythmias in the absence of digoxin therapy. The safety database is also deficient in terms of describing the consequences of chronic administration of digoxin to a pediatric population in terms of growth and development.

E. Summary of Critical Safety Findings and Limitations of Data

The most well described form of digoxin toxicity in pediatric populations is cardiac/electrocardiographic toxicity. Some of the types of cardiac toxicity that have been reported include sinus node depression with escape rhythms, atrio-ventricular block, ventricular fibrillation, premature ventricular contractions, nodal tachycardias, severe bradycardia, and paroxysmal atrial tachycardia. Non-cardiac forms of toxicity have been reported but much less frequently. The evaluation of non-cardiac forms of toxicity can be difficult especially among neonates and infants that have not developed skills to verbalize complaints. Examples of non-cardiac toxicity that have been reported include vomiting and poor feeding.

The identification of potentially serious cardiac toxicity with this formulation and no convincing evidence of efficacy is very concerning. The benefit to risk ratio will be pivotal in deciding whether to approve or not to approve this formulation.

VIII. Dosing, Regimen, and Administration Issues

A study by Bakir et. al. evaluated the effects of dosing regimen on infants and children receiving digoxin[41]. The majority of the 30 patients included in the study had congenital heart disease and were being treated with digoxin administered twice a day for at least 20 days. Patients were in stable clinical condition on constant doses of digoxin. Fifteen of the 30 patients in this study were randomly assigned to receive their usual twice a day dose as one single dose administered once a day(treatment group). The other 15 subjects (control group) continued their usual dosing regimen. Comparisons of the peak and trough serum digoxin levels were made at steady state. In the treatment group, trough concentrations were 1.0 ng/mL and 0.8 ng/mL for twice a day dosing and once a day dosing respectively. Peak concentrations (2 hours post treatment) were 1.6 ng/mL and 2.3 ng/mL for the twice a day dosing and once a day dosing respectively. Toxic symptoms were not observed clinically and clinical assessments did not significantly change in any patient. The conclusions of this study are that once a day dosing versus twice a day dosing does not alter either the efficacy or toxicity profile of digoxin. It is likely that this study was under-powered to detect any efficacy or toxicity issues as a function of dosing regimen.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

N/A

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

N/A

C. Evaluation of Pediatric Program

The focus of this review is on the use of digoxin in a pediatric population

D. Comments on Data Available or Needed in Other Populations

N/A

X. Conclusions and Recommendations

A. Conclusions

In this supplemental NDA, the Agency is specifically seeking evidence efficacy and safety justifying the use of digoxin in a pediatric population. The use of digoxin in adults is adequately characterized and because of this, NDA #20-045 for digoxin tablets was approved in 1994. At that time, the basis for pediatric dosing of digoxin tablets was not formally reviewed. For the current submission, justification for the efficacy and safety of digoxin in pediatric populations is much more critical because of the nature of the formulation: that of an elixir.

A careful review of the submitted references along with an independent search of the peer reviewed medical literature does not support the current labeling in a pediatric population. There are no randomized, placebo controlled, blinded studies, evaluating outcomes of clinical importance. Many of the studies of the studies done in congestive heart failure in various pediatric populations have major faults e.g. small numbers of subjects, no control or baseline control groups, unblinded, evaluating echocardiographic endpoints (rather than clinical), etc. No prospective studies have been found that evaluate the role of digoxin in pediatric arrhythmias. All the studies of the use of digoxin in pediatric arrhythmias are retrospective.

B. Recommendations

I believe that there are 3 available options. The first option is to do nothing which I don't believe supports the Agency's mission of ensuring that safe and effective drugs are on the market. The process of reviewing the peer reviewed medical literature has shown that there is no justification for the current digoxin elixir labeling in a pediatric population. It make little sense for the Agency to allow marketing of a drug for a population in whom efficacy is not clearly established and for which the risk of toxicity is real.

The second option is to remove dosing recommendations for pediatric populations and explicitly state in the label that there are no adequate data in the peer reviewed medical literature that support efficacy in that population. In this scenario, digoxin elixir would be approved for use in adult patients that can't swallow (e.g. intubated patients, patients with G-tube in place secondary to stroke or upper GI pathology) in which case safety and efficacy information could be referenced from the tablet. This could be an acceptable alternative provided that pediatricians do not begin to use digoxin elixir "off-label".

The third option is to have the Sponsor conduct adequate and well controlled trials that conform to the standards used by the Agency today. I believe this is the best option but one that is not so easy to do. Some of the barriers to completing such a trial would be convincing parents to enroll their children in a placebo controlled trial. From an ethical perspective, this would be possible because there is inadequate data that digoxin has any efficacy in this population. The difficulties of doing such a clinical trial in children would involve choosing what endpoints to use. In adults, digoxin is indicated to reduce symptoms of heart failure and to control ventricular response rate in patients with chronic atrial fibrillation. Symptomatic endpoints such as these would be nearly impossible to adequately evaluate in a pediatric population involving neonates or toddlers. Reducing hospital stay could be another possible endpoint. With respect to atrial fibrillation, it is a rather uncommon arrhythmia in this population. In considering a pediatric clinical trial for heart failure or atrial fibrillation, the key question would be whether it is practical to enroll enough pediatric patients so that there would be adequate power to detect an effect. A pharmacokinetic/ pharmacodynamic study could be an option except for the fact that the pathophysiology of heart failure is sufficiently different in adults and children to make extrapolation very difficult. A PK/PD study could be an option if sufficient numbers of children with atrial fibrillation could be enrolled. In this scenario, heart rate could serve as a potential surrogate.

This application is approvable given that one of the latter two options presented above can be met.

XI. Appendix

A. Other Relevant Materials

Appendix Table 1: Digitalizing and maintenance dose recommendations in children with normal renal function based on lean body weight as stated in the Lanoxin Pediatric Elixir Label.

Age	Oral digitalizing dose (μg/kg)	Daily maintenance dose (μg/kg)
Premature	20 to 30	20% to 30 % or oral digitalizing dose
Full-term	25 to 35	
1 to 24 months	35 to 60	25% to 35% of oral digitalizing dose
2 to 5 years	30 to 40	
5 to 10 years	20 to 35	
Over 10 years	10 to 15	

Appendix Table 2: Daily maintenance doses in children with normal renal function as stated in Lanoxin tablet table.

Age	Daily maintenance dose (μg/kg)
2 to 5 years	10 to 15
5 to 10 years	7 to 10
Over 10 years	3 to 5

B. Individual More Detailed Study Reviews (If performed)

N/A

References

1) The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. NEJM. 1997; 336(8): 525-33.
2) Kay JD, Colan SD, Graham TP,. Congestive Heart failure in pediatric patients. Am Heart Journal 2001; 142:923-8.
3) Luedtke SA, Kuhn RJ, McCaffrey F. Pharmacologic management of supraventricular tachycardias in children. Part 2: Atrial flutter, atrial fibrillation, and junctional and atrial ectopic tachycardia. Ann Pharmacother 1997; 31(11): 1347-59.
4) Luedtke SA, Kuhn RJ, McCaffrey F. Pharmacologic management of supraventricular tachycardias in children. Part 1: Wolff-Parkinson-White and atrioventricular nodal reentry. Ann Pharmacother 1997; 31(10): 1227-43.
5) Wettrell G, Andersson KE. Absorption of digoxin in infants. Eur J Clin Pharmacol. 1975;9:49-55.
6) Hastreiter AR, John EG, van der Horst RL. Digitalis, digitalis antibodies, digitalis-like immunoreactive substances, and sodium homeostasis: a review. Clin Perinatol. 1988;15:491-522.
7) Wells TG, Young RA, Kearns GL. Age-related differences in digoxin toxicity and its treatment. Drug Saf. 1992;7:135-51.
8) Park MK, Ludden T, Arom KV, Rogers J, Oswalt JD. Myocardial vs serum digoxin concentrations in infants and adults. Am J Dis.Child. 1982;136:418-20.
9) Hastreiter AR, van der Horst RL, Voda C, Chow-Tung E. Maintenance digoxin dosage and steady-state plasma concentration in infants and children. J Pediatr. 1985;107:140-146.
10) Koren G, Parker R. Interpretation of excessive serum concentrations of digoxin in children. Am J Cardiol. 1985;55:1210-1214.
11) Pudek MR, Seccombe DW, Humphries K. Digoxin-like immunoreactive substances and bile acids in the serum of patients with liver disease. Clin Chem. 1986;32:2005-6.
12) Silber B, Sheiner LB, Powers JL, Winter ME, Sadee W. Spironolactone-associated digoxin radioimmunoassay interference. Clin Chem. 1979;25:48-50.
13) Valdes R Jr, Graves SW, Brown BA, Landt M. Endogenous substance in newborn infants causing false positive digoxin measurements. J Pediatr. 1983;102:947-50.
14) Datta P, Xu L, Malik S, Landicho D, Ferreri L, Halverson K et al. Effect of antibody specificity on results of selected digoxin immunoassays among various clinical groups. Clin Chem. 1996;42:373-9.
15) Jiang F, Wilhite TR, Smith CH, Landt M. A new digoxin immunoassay substantially free of interference by digoxin immunoreactive factor. Ther Drug Monit. 1995;17:184-8.
16) Kimball TR, Daniels SR, Meyer RA, Hannon DW, Tian J, Shukla R et al. Effect of digoxin on contractility and symptoms in infants with a large ventricular septal defect. Am J Cardiol. 1991;68:1377-82.
17) Hofstetter R, Lang D, von Bernuth G. Effect of digoxin on left ventricular contractility in newborns and infants estimated by echocardiography. Eur J Cardiol. 1979;9:1-11.
18) Nadas AS, Rudolph AM, Reinhold JDL. The use of digitalis in infants and children: a clinical study of patients in congestive heart failure. N Engl J Med. 1953;248:98-105.

19) Sandor GG, Bloom KR, Izukawa T, Patterson MW, Rowe RD. Noninvasive assessment of left ventricular function related to serum digoxin levels in neonates. Pediatrics. 1980;65:541-6.
20) Berman W, Yabek SM, Dillon T, Niland C, Corlew S, Christensen D et al. Effects of digoxin in infants with congested circulatory state due to a ventricular septal defect. N.Engl.J Med. 1983;308:363-66.
21) Seguchi M, Nakazawa M, Momma K. Further evidence suggesting a limited role of digitalis in infants with circulatory congestion secondary to large ventricular septal defect. Am J Cardiol. 1999;83:1408-11, A8.
22) Lundell BP, Boreus LO. Digoxin therapy and left ventricular performance in premature infants with patent ductus arteriosus. Acta Paediatr.Scand. 1983;72:339-43.
23) Pfammatter JP, Stocker FP. Re-entrant supraventricular tachycardia in infancy: current role of prophylactic digoxin treatment. Eur J Pediatr. 1998;157:101-6.
24) Garson A, Gillette PC, McNamara DG. Supraventricular tachycardia in children: clinical features, response to treatment, and long-term follow-up in 217 patients. J Pediatr. 1981;98:875-82.
25) Deal BJ, Keane JF, Gillette PC, Garson A. Wolff-Parkinson-White syndrome and supraventricular tachycardia during infancy: management and follow-up. J Am Coll.Cardiol. 1985;5:130-135.
26) Garson A Jr, Bink-Boelkens M, Hesslein PS, Hordof AJ, Keane JF, Neches WH et al. Atrial flutter in the young: a collaborative study of 380 cases. J Am Coll Cardiol. 1985;6:871-8.
27) Lubbers WJ, Losekoot TG, Anderson RH, Wellens HJ. Paroxysmal supraventricular tachycardia in infancy and childhood. Eur J Cardiol. 1974;2:91-99.
28) Koike K, Hesslein PS, Finlay CD, Williams WG, Izukawa T, Freedom RM. Atrial automatic tachycardia in children. Am J Cardiol. 1988;61:1127-30.
29) Soyeur DJ. Atrial flutter in the human fetus: diagnosis, hemodynamic consequences, and therapy. J Cardiovasc Electrophysiol. 1996;7:989-98.
30) Mendelsohn A, Dick M 2nd, Serwer GA. Natural history of isolated atrial flutter in infancy. J Pediatr. 1991;119:386-91.
31) Levine OR, Blumenthal S Digoxin dosage in premature infants. Pediatrics. 1962; 29(1):18-25.
32) Levine OR, Somlyo AP. Digitalis intoxication in premature infants. J of Pediatrics. 1962;61(1):70-8.
33) Larese RJ, Mirkin BL Kinetics of digoxin absorption and relation of serum levels to cardiac arrhythmias in children. Clin Pharmacol Ther. 1974;15(4):387-96.
34) Krasula R, Yanagi R, Hastreiter AR, Levitsky S, Soyka LF. Digoxin intoxication in infants and children: correlation with serum levels. J Pediatr. 1974;84:265-9.
35) Hayes CJ, Butler VP Jr, Gersony WM. Serum digoxin studies in infants and children. Pediatrics. 1973;52:561-8.
36) Neutze JM, Rutherford JD, Hurley PJ. Serum digoxin concentrations in neonates, infants and children with heart disease. N.Z. Med J. 1977;86:7-10.
37) Berman W, Dubynsky O, Whitman V, Friedman Z, Maisels MJ. Digoxin therapy in low-birth-weight infants with patent ductus arteriosus. J Pediatr. 1978;93:652-55.

38) Halkin H, Radomsky M, Blieden L, Frand M, Millman P, Boichis H. Steady state serum digoxin concentration in relation to digitalis toxicity in neonates and infants. Pediatrics. 1978;61:184-8.

39) Pinsky WW, Jacobsen JR, Gillette PC, Adams J, Monroe L, McNamara DG. Dosage of digoxin in premature infants. J Pediatr. 1979;94:639-42.

40) Iisalo E, Dahl M, Sundqvist H. Serum digoxin in adults and children. Int.J Clin Pharmacol. 1973;7:219-22.

41) Bakir M, Bilgic A. Single daily dose of digoxin for maintenance therapy of infants and children with cardiac disease: is it reliable? Pediatr Cardiol. 1994;15:229-32.

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