COMPARATIVE ANALYSIS OF PLASMA CONCENTRATIONS IN ONCE-A-DAY VERSUS TWICE-A-DAY DIGOXIN REGIMEN IN PEDIATRIC PATIENTS

by

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A project submitted to the faculty of the
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for the degree of

Doctor of Pharmacy

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UNIVERSITY OF UTAH COLLEGE OF PHARMACY

FINAL READING APPROVAL

TO THE DOCTOR OF PHARMACY COMMITTEE OF THE UNIVERSITY OF UTAH COLLEGE OF PHARMACY:

I have read the clinical research project report of Rachel L. Klieman in its final form and have found that 1) its format, citations, and bibliographic style are consistent and acceptable; 2) its illustrative materials including figures, tables, and charts are in place; and 3) the final manuscript is satisfactory to the Supervisory Committee and is ready for submission to the Doctor of Pharmacy Committee.

11/3/83
Date

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UNIVERSITY OF UTAH COLLEGE OF PHARMACY

SUPERVISORY COMMITTEE APPROVAL

of a clinical research project report submitted by

Rachel L. Klieman

We, the undersigned, have read this clinical research project report and have found it to be of satisfactory quality for a Doctor of Pharmacy Degree.

11/3/83
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Chairman, Supervisory Committee

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Date

Member, Supervisory Committee

ACKNOWLEDGEMENTS

I would like to thank my Supervisory Committee, Dr. John Bosso, Dr. Jean Nappi, and Dr. Herbert Ruttenberg, for the time they have given in evaluating my final research report.

To my dearest mother, Sara, my brother, Jacob, a very special thanks for their continuous support and encouragement.

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BACKGROUND

Digoxin is a valuable drug for a variety of cardiovascular disorders but is known to have a low margin of safety. While digoxin is used in pediatric patients for several cardiac conditions,[1] there is some controversy over the most appropriate dose and dosage regimen.[2] These are based on presumed differences in digoxin disposition and dose response relationships in infants and children as compared to adults.[1,2] Two basic differences exist in the use of digoxin in children and adults. Children receive higher daily doses (based on body weight) and commonly receive the drug as two, rather than one, daily dose.

Sensitivity Studies

The basis for the age related differences in sensitivity to digoxin apparently involves several factors. Cardiac glycosides bind to and inhibit the transport enzyme sodium-potassium adenosine triphosphatase (Na-K ATPase) in different tissues. The degree of this binding may be age related. Miller and Gilliland demonstrated that median myocardial Na-K ATPase concentration was significantly greater in fetal and newborn puppies than in mature dogs, which may be an explanation for the higher digoxin concentration in the heart of the newborn.[3]

Postmortem concentrations of digoxin in ventricular and atrial tissues of infants (up to 12 months of age) are much higher than those in adults.[4] However, an analysis of tissues taken postmortem from

both infants and adults showed the same relative distribution in infants and adults (choroid plexus > ventricular myocardium > kidney > liver > skeletal muscle).[4] A lower concentration is found in the blood.[2,5] The average digoxin concentration in infants' ventricular myocardium was 190 ng/g of body weight in contrast to 70 ng/g of body weight in older children with ratios of ventricular myocardium to plasma concentrations of 99:1 in infants and 114:1 in older children.[4] Such data support the theory that myocardial tissue shows greater affinity for digoxin but decreased sensitivity in pediatric as compared to adult patients.

Dose response curves obtained with neonatal myocardium are shifted to the right of those generated in adult rabbits.[6] That is, a larger dose is required to induce the same response in newborn as in adult rabbits.

Efficacy Studies

Levy used systolic time intervals as a measure of digoxin effect on cardiac contractility in neonates (up to one month of age) and infants. He observed satisfactory responses with much lower loading doses than those conventionally used.[7] Instead of 80 mcg/kg, he used 20-30 mcg/kg and concluded that higher dosages were unwarranted and produced no further changes in preejection period or ejection time.[7] This finding was supported in the reports of Nyberg[8] and Neutze,[9] which showed adequate positive inotropic effect at serum digoxin concentrations of 1.4 to 2.6 ng/ml, at doses of 18 and 22 mcg/kg/day, respectively.

Toxicity Studies

While the results of many clinical studies suggest that infants and young children can tolerate higher doses of digoxin per unit body weight than adults,[5,8,10-16] this finding was not duplicated by others. Hayes[15] studied 31 infants, 1 to 11 months of age, who received maintenance doses of 14 to 28 mcg/kg/day, 33 children 2 to 14 years of age who received maintenance doses of 10 to 17 mcg/kg/day in younger children (under the age of five years) while the older children were given 6 to 10 mcg/kg/day and 24 adults who received maintenance doses of 1.3 to 11.5 mcg/kg/day. These doses produced mean serum digoxin concentrations of 2.8 ± 1.9 ng/ml, 1.3 ± 0.4 ng/ml and 1.3 ± 0.6 ng/ml, respectively. Five infants, ten children and four adults manifested arrhythmias compatible with digoxin toxicity. The mean serum concentrations in those patients were 4.4 ng/ml, 3.4 ng/ml, and 2.9 ng/ml, respectively. Halkin[17] studied 34 patients ranging in age from one week to two years. All patients who manifested symptoms of digoxin intoxication were less than one year of age. Thirteen of 34 patients had serum digoxin concentrations higher than 2 ng/ml and four of the 13 had signs of toxicity according to the criteria of Beller et al[18] (appearance of specific electrocardiogram findings such as: premature ventricular contractions, ventricular bigeminy, A-V escape rhythm, A-V dissociation, and Mobitz Type I conduction disturbance). These results support the theory that digoxin serum concentrations higher than 2 ng/ml which are generally considered dangerous in adults but which are commonly considered safe in children can cause increased toxicity in pediatric patients.[17]

Pharmacokinetics

The biopharmaceutics and pharmacokinetics of digoxin in pediatric patients have been studied. A number of investigators have found that infants receiving oral maintenance therapy absorbed the drug as well as adults, and that the time to reach peak blood concentrations varied from 1 to 3 hours.[1,2,6,12,19]

The mean apparent volume of distribution (Vd) of digoxin has been shown to vary between neonates, infants and adults. Neonates and infants have a larger Vd than adults (9 vs 6 1/kg, respectively). The reason for this difference is unclear, but might be attributable to greater tissue binding and to age-related differences in body composition (extracellular fluid volume and ratio of tissue weight/body weight).[2,10,20] The distribution of digoxin includes its excretion into saliva. Huffman[21] found that there was significant correlation between the serum and saliva levels but other investigators' data did not support this conclusion.[22,23,24]

Studies in adults have shown that digoxin is eliminated mainly unchanged through the kidney by glomerular filtration. The percentage of various metabolites (non-renal elimination) excreted in the urine by patients with normal hepatic and renal function is 12 to 18 percent in both pediatric and adult populations. The total body elimination half-life ($t_{\frac{1}{2}}$) in neonates ranges from 20 to 60 hours with the mean being approximately 35 hours.[13,20] The $t_{\frac{1}{2}}$ in infants ranges from 15 to 33 hours with a mean of 20 hours.[20,25] In children, it ranges from 17 to 52 hours with a mean of 35 hours.[6,13] In adults, the mean serum half-life is 33 hours.[26] Thus, the only pediatric group that is appreciably different from adults are infants.

Total body clearance (Cl_b) of digoxin in these same populations shows similar diversity with values of 25 to 65 and 75 to 236 ml/min/1.73m^2 in neonates and infants, respectively. These large ranges in $t_{\frac{1}{2}}$ and Cl_b have been explained as a function of developmental changes in renal glomerular function which alter renal clearance of digoxin with increasing age.[27-29] By four to six months of age, the total body clearance rate approximates that of adults.[2,6,20]

Thus, on a pharmacokinetic basis, there appears to be little reason to dose digoxin any differently in children than in adults; that is, a once-a-day regimen instead of a twice-a-day regimen should be adequate. However, it is common practice to dose children every 12 hours.

STUDY OBJECTIVES

There were two objectives to this study. The primary objective was to investigate if there was a significant difference in digoxin serum concentration obtained with once-a-day and twice-a-day digoxin administration regimens. This was done by comparing serum concentrations of digoxin achieved by once-a-day and twice-a-day dosing.

A secondary objective was to evaluate the relationship between serum and salivary concentrations of digoxin.

MATERIALS AND METHODS

Design

The study used a crossover design with each patient serving as his or her own control.

Patient Population

The population consisted of six outpatients from the Cardiology Clinic at Primary Children's Medical Center. The range of ages was 4 to 19 years with a mean of 8.3. Three subjects were male and three were female, weighing between 13 and 53 kg with a mean weight of 26.4 ± 19.4 kg (Table 1). All patients were receiving oral digoxin on a twice-a-day schedule prior to entry into the study. Informed written consent was obtained from the parents of each patient judged to be suitable for entry into the study (Appendix A).

Methods

Parents kept daily records of times doses were given and exact pill counts were taken prior to and at the end of the study (Appendix B).

Upon entering the study, serum and saliva samples were obtained from each patient eight hours after the last reported dose. All patients maintained their twice-a-day digoxin dosing schedule for a minimum of 14 days to assure that steady state serum concentrations had been attained. After this time period, serum and saliva samples were obtained eight hours after the last reported dose. Each patient was then scheduled to receive a single daily dose using the same total daily dose of digoxin. This schedule was maintained for a minimum of 14 days with daily recording by the parents of specific times each dose was administered. At the end of the second study period, serum and saliva samples were again obtained eight hours after the last reported dose. After the study, all patients were switched back to twice-a-day digoxin administration.

Saliva samples (1 ml) were drawn in plastic syringes and then put into plastic freezing tubes and stored at -70°C. Blood samples, drawn into silicone coated tubes (red top Vacutainers®, Becton-Dickinson, Rutherford, N.J.) were centrifuged for five minutes at 2,500 RPM and the serum was removed and stored at -70°C, until they were assayed for digoxin concentration in the clinical laboratory of Primary Children's Medical Center.

Digoxin Assay

Each saliva sample was divided in half and the duplicate samples were extracted with 0.2 ml of chloroform ($CHCl_3$) by gentle shaking for ten minutes. After centrifugation, the aqueous phase was removed. Duplicate 0.8 ml aliquots of $CHCl_3$ extract were obtained and dried under air at 45°C. The dried $CHCl_3$ extract was dissolved in 0.2 ml blank serum and assayed by radioimmunoassay for digoxin concentration along with the patients' serum.

Digoxin concentrations were determined by the RIAphase Digoxin Reagent System® (Beckman Instruments, Inc., Berkely, California) designed for the quantitative radioimmunoassay of digoxin as described by Smith.[30] The method's lowest level of sensitivity was 0.2 ng/ml. The percent difference between the standard curve and the actual readings ranged from -16.6 to +13.8 percent.

This procedure utilizes I^{125} labeled digoxin (I.D.) as the tracer and digoxin-specific antibodies capable of binding both unlabeled digoxin (U.D.) and I.D. After conventional incubation of antibody with serum and binding equilibration of I.D. and U.D. with antibody, the solution is passed through a chamber containing an excess of

immunoadsorbent bound to cellulose. The I.D. and U.D. not bound to antibody is bound in this chamber and the bound I.D. and U.D. passed out, where radioactivity is measured by a gamma counter. After a wash-out of the immunoadsorbent chamber to determine the percent of I.D., the value is compared to a standard curve.

STATISTICAL ANALYSIS

The Wilcoxin matched-pairs signed-ranks test was used to determine if there was a statistically significant difference between digoxin serum concentration levels produced by the two dosage schedules.[31] Linear regression was used to evaluate the relationship between serum and saliva digoxin concentrations.

RESULTS

The patients' doses ranged from 4.7 to 12.2 mcg/kg/day with a mean of 8.9 ± 3.2 mcg/kg/day (Table 2). Results of the serum and saliva concentration determinations are presented in Tables 3 and 4. Changes in serum digoxin concentration produced by the different dosing regimens is illustrated in Figure 1. The intrapatient difference between the two dosing regimens (using digoxin concentrations from weeks two and four) did not show a statistically significant difference ($T = 8$, $p > 0.05$). The mean serum digoxin concentration (± standard deviation) of twice-a-day dosing was 0.63 ± 0.15, and of once-a-day dosing was 0.76 ± 0.38 ng/ml. The range of the difference of serum digoxin between the two regimens ranged from -29 to +143 percent.

Patient number 3 missed four appointments and his parents' compliance and understanding of the study was questionable. This patient's

serum digoxin concentration was also much higher than expected. That could be due to the drug being administered at a time different than reported. Therefore the study data were also analzyed with the patient 3 data deleted. After excluding his data, the above calculations were performed again. Again the intrapatient difference between the two dosing regimens did not show a statistically significant difference ($T = 7$, $p > 0.05$) and the range of the difference of serum digoxin between the two regimens was -29 to +51 percent. None of the patients experienced any clinical signs of toxicity.

Linear regression was performed to evaluate the relationship between the serum and saliva digoxin concentrations (Figure 2). The resultant correlation coefficient ($r = 0.651$) was significant ($df = 15$, $\alpha < 0.005$), the equation describing the best line is $y = 0.612x + 0.308$, with variable x = saliva concentration, and variable y = serum concentrations. The range of the difference of digoxin concentration between serum and saliva ranges from -64 to +65 percent. Visual inspection of Figure 2 reveals considerable scatter, so that the use of this relationship may be unreliable.

Compliance was judged with the assistance of the "patient's daily record" forms (Appendix B) and exact pill counts. According to these records all patients had 100 percent compliance except patient 1, whose compliance was 85 percent. However, as noted above, the compliance of patient 3 was questionable.

DISCUSSION

Digoxin is often used in the pediatric population. The literature provides conflicting information concerning the most appropriate dosing

regimen of digoxin in children.[5] Data demonstrating an age dependent rate of digoxin elimination from the neonate period through childhood have been published by various researchers. Lang[13] and Wettrell[20] found that neonates have a digoxin elimination half-life between 20 and 60 hours. Wettrell[20] and Dungan[25] evaluated digoxin kinetics in infants and found it to range from 15 to 33 hours. Singh[6] and Lang[13] found that children have a digoxin elimination half-life of 15 to 52 hours. On the basis of the long half-life, it seems reasonable to administer digoxin once daily in children. This is supported by our data which demonstrate no statistically significant difference between eight hour serum levels produced by the two dosing regimens. It should be noted, however, that intrapatient differences with the two dosing regimens were often large. While these differences were not clinically significant according to clinical evaluation by a pediatric cardiologist, the possibility exists that toxicity or loss of therapeutic response could occur with such large changes. While some patients' digoxin concentrations were higher on the once-a-day schedule, others were lower. This may be due to interpatient differences in absorption rate, the length of the drug distribution phase or the interval between the blood draw and the administration of the last dose. It should also be noted that there was no clinical evidence of toxicity or loss of therapeutic response when the patients changed from one regimen to the other.

Further, one may approximate maximum and minimum digoxin concentrations produced by the same dose given once-a-day or as two divided doses, using the relationships:

$$C_{p\ min_{ss}} = \frac{Dose \cdot e^{-K_{el} \cdot t}}{Vd(1 - e^{-K_{el} \cdot t})}$$

$$C_{p\ max_{ss}} = \frac{Dose}{Vd\ (1 - e^{-K_{el} \cdot t})}$$

where t = dosage interval, and using reported pharmacokinetic parameters for children, (Vd=9 l/kg, K_{el}=0.0198 hr^{-1}, Dose=3 mcg/kg/day). On a once-a-day digoxin regimen (t=24 hours), $C_{p\ min_{ss}}$=0.54 ng/ml, and $C_{p\ max_{ss}}$=0.86 ng/ml. With a twice-a-day digoxin regimen (t= 12 hours), $C_{p\ min_{ss}}$=0.62 ng/ml and $C_{p\ max_{ss}}$ = 0.78 ng/ml. There was little difference between the digoxin serum concentration produced by the two dosing regimens. It is recognized that these equations assume I.V. bolus dosing and a one compartment open model, neither of which hold for orally administered digoxin. Nonetheless, the basic principles apply and are cogent to our argument. Thus we can see no basis for twice-a-day dosing in children.

Performing the same calculations for infants as they comprise the only pediatric group with mean half-life different from that of adults, using K_{el} of 0.035 hr^{-1}, $C_{p\ max_{ss}}$, and $C_{p\ min_{ss}}$, the values for the once-a-day or twice-a-day regimen were 0.59 and 0.26 ng/ml, and 0.49 and 0.32 ng/ml, respectively. Once again we see little difference between the dosing regimens and no basis for twice-a-day dosing in infants or children.

All parents stated that it was much easier to remember the once daily dose rather than the twice daily dose, the former regimen being

more convenient. Our results suggest that it may be appropriate to recommend once daily dosing of digoxin, which will be more convenient and provide adequate serum concentrations.

Huffman found an excellent linear correlation between serum and saliva digoxin concentration ($r = 0.988$)[21] but this finding was not supported by Krivoy[23] who reported the correlation coefficient to be 0.71, or by Buchanan[22] who reported a correlation coefficient of 0.41. Our data analysis demonstrated a significant correlation of 0.651 ($p < 0.005$) but too much scatter for this relationship to be used as a reliable clinical tool. The determination of saliva digoxin in children is easy and noninvasive, and appears to be an alternative to blood sampling, when blood sampling is difficult or not possible. Our findings did not demonstrate a consistent relationship, therefore the use of saliva in place of serum determinations cannot be recommended on a routine basis.

CONCLUSIONS

Pediatric patients in this study required higher doses on a mcg/kg basis than do adults to achieve plasma concentrations that are considered therapeutic in adults. There is no evidence that children are less sensitive to digoxin than are adults. Calculations performed on data from this study as well as theoretical data, showed that there was no statistically significant difference between a once-a-day regimen and a twice-a-day regimen. Intrapatient differences, however, could be clinically important.

The relationship between serum and saliva digoxin concentration was statistically significant, but showed considerable variation and cannot be recommended to replace serum concentration determinations based on the data obtained.

TABLES

TABLE 1. Characteristics of the Patient

Patient	Sex	Age (yrs)	Weight (kg)	Diagnosis
1	M	11	50.0	Tricuspid atresia with Glen Anastomosis and Blalock - Taussig shunt
2	F	19	53.0	Truncus arteriosus Eisenmenger Syndrome
3	M	4	14.8	Tetralogy of fallot - repaired
4	F	5	13.8	Subaortic stenosis - repaired with artificial mitral valve
5	F	5	13.0	Single ventricle with pulmonary atresia, Blalock - Taussig shunt
6	M	6	14.0	Single ventricle with pulmonary stenosis and Blalock - Taussig shunt

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5	F	5	13.0	Single ventricle with pulmonary atresia, Blalock - Taussig shunt
6	M	6	14.0	Single ventricle with pulmonary stenosis and Blalock - Taussig shunt

TABLE 2. Patients Digoxin Dosing Regimens

Patient	Digoxin Dose (mg)	Digoxin Dose (mcg/kg/day)
1	0.125 BID 0.250 QD	5.0
2	0.125 BID 0.250 QD	4.7
3	0.09 BID 0.18 QD	12.2
4	0.07 BID 0.14 QD	10.1
5	0.065 BID 0.13 QD	10.0
6	0.08 BID 0.16 QD	11.4
Mean ± Standard Deviation		8.9 ± 3.2

TABLE 3. Patient's Serum Levels

Patient	Digoxin Regimen	Serum Digoxin (ng/ml)	% Difference of Serum Digoxin*
1	BID	< 0.15	
	BID	0.51	
	QD	0.36	- 29
2	BID	0.75	
	BID	0.56	
	QD	0.59	+ 5
3	BID	0.29	
	BID	0.56	
	QD	1.36	+143
4	BID	0.60	
	BID	0.54	
	QD	0.52	- 4
5	BID	0.74	
	BID	0.71	
	QD	1.07	+ 51
6	BID	0.86	
	BID	0.91	
	QD	0.65	- 29
Mean			+ 23

* % Difference of serum digoxin was calculated using the second figure of twice-a-day and once-a-day digoxin regimen.

TABLE 4. Patient's Serum and Saliva Levels

Patient	Serum Digoxin (ng/ml)	Saliva Digoxin (ng/ml)	% Difference between Serum and Saliva
1	< 0.15	< 0.15	
	0.51	0.42	- 18
	0.36	0.33	- 8
2	0.75	0.83	+ 11
	0.56	0.57	+ 2
	0.59	0.78	+ 32
3	0.29	0.25	- 14
	0.56	0.51	- 9
	1.36	1.32	- 3
4	0.60	0.53	- 12
	0.54	0.89	+ 65
	0.52	0.40	- 23
5	0.74	0.56	- 24
	0.71	0.70	- 1
	1.07	0.38	- 64
6	0.86	0.52	- 40
	0.91	0.98	+ 8
	0.65	0.39	- 40
Mean ± Standard Deviation			- 8 ± 29

FIGURES

Figure 1. COMPARISON OF CHANGE IN SERUM DIGOXIN CONCENTRATION

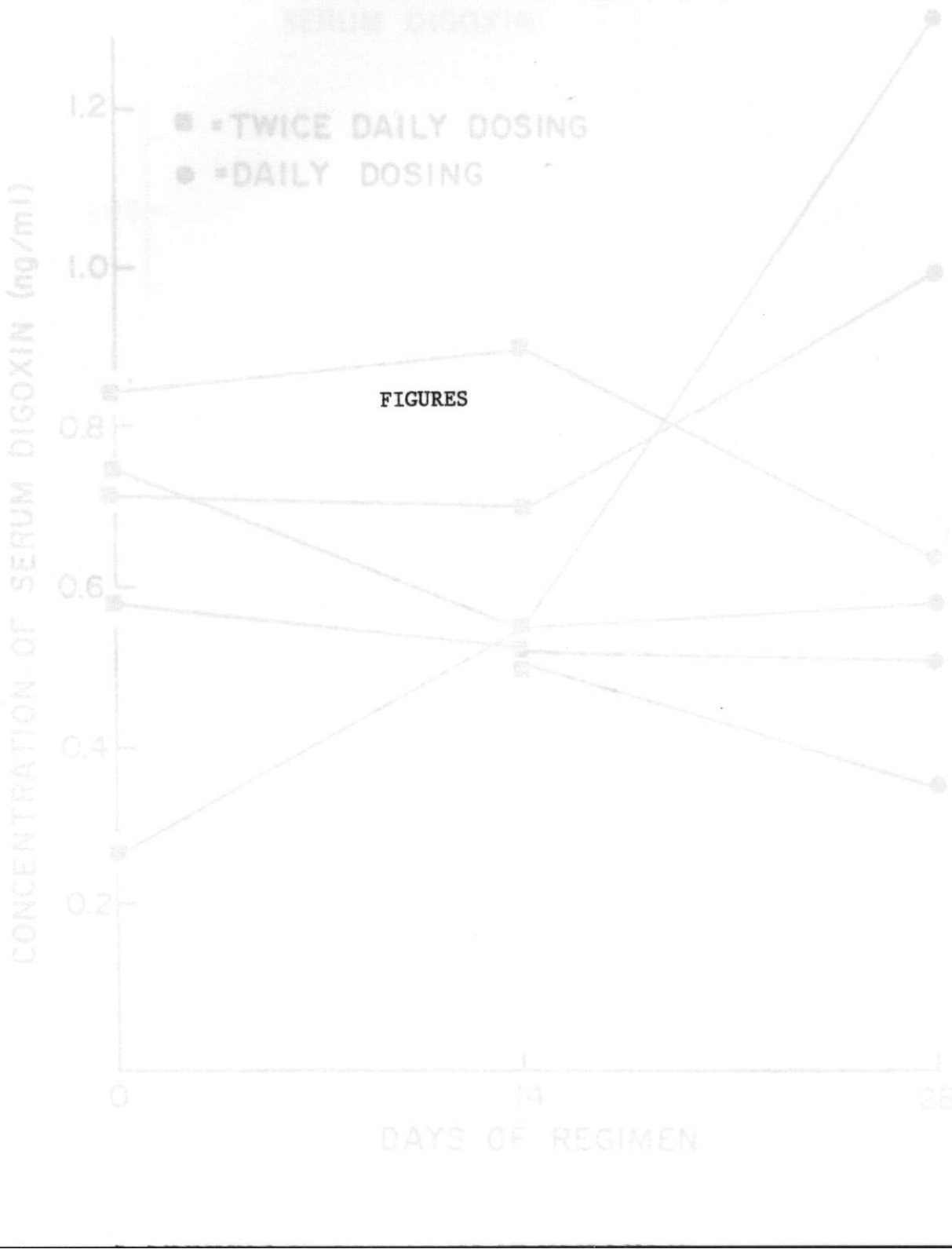


Figure 1. COMPARISON OF CHANGE IN SERUM DIGOXIN CONCENTRATION

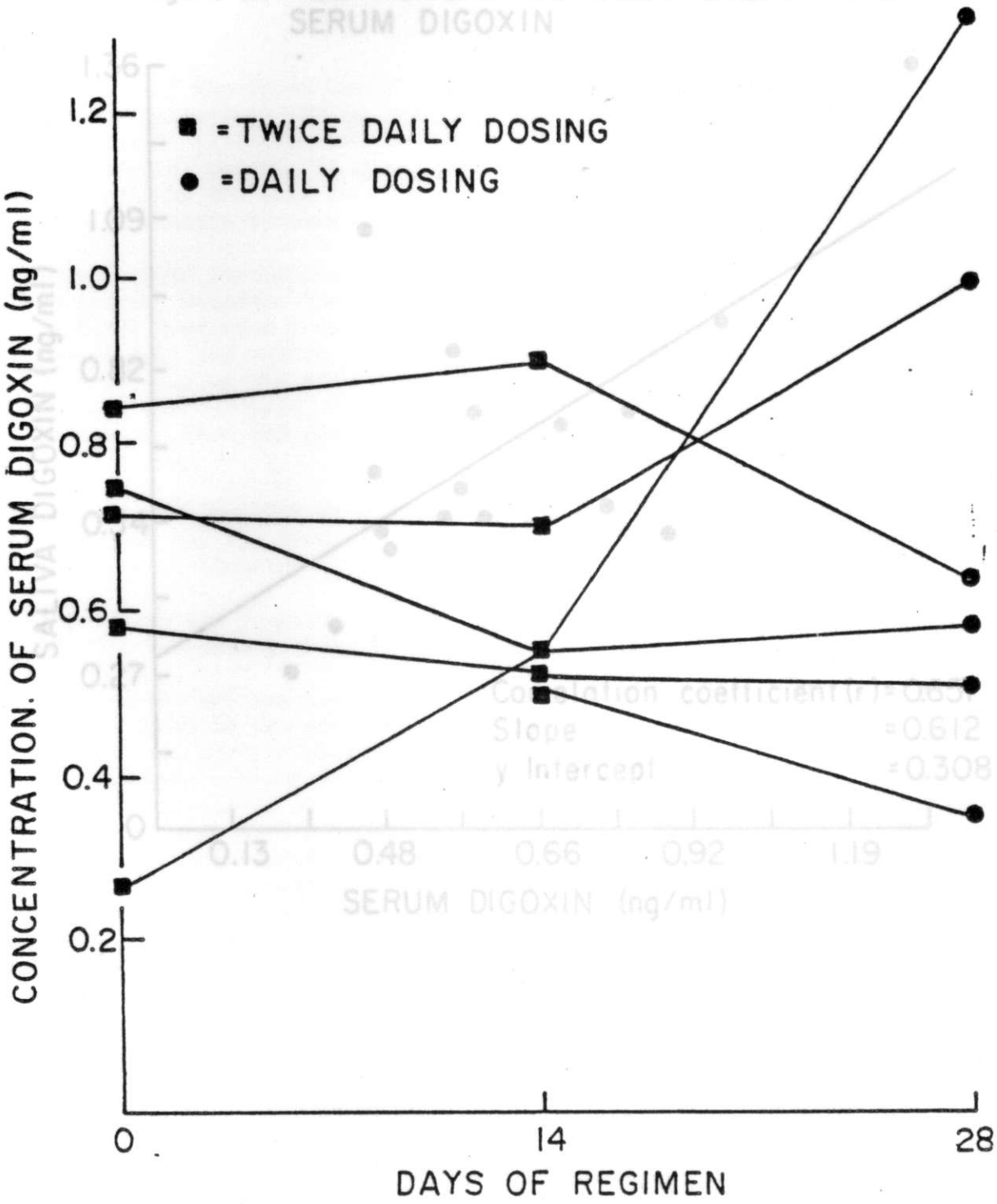
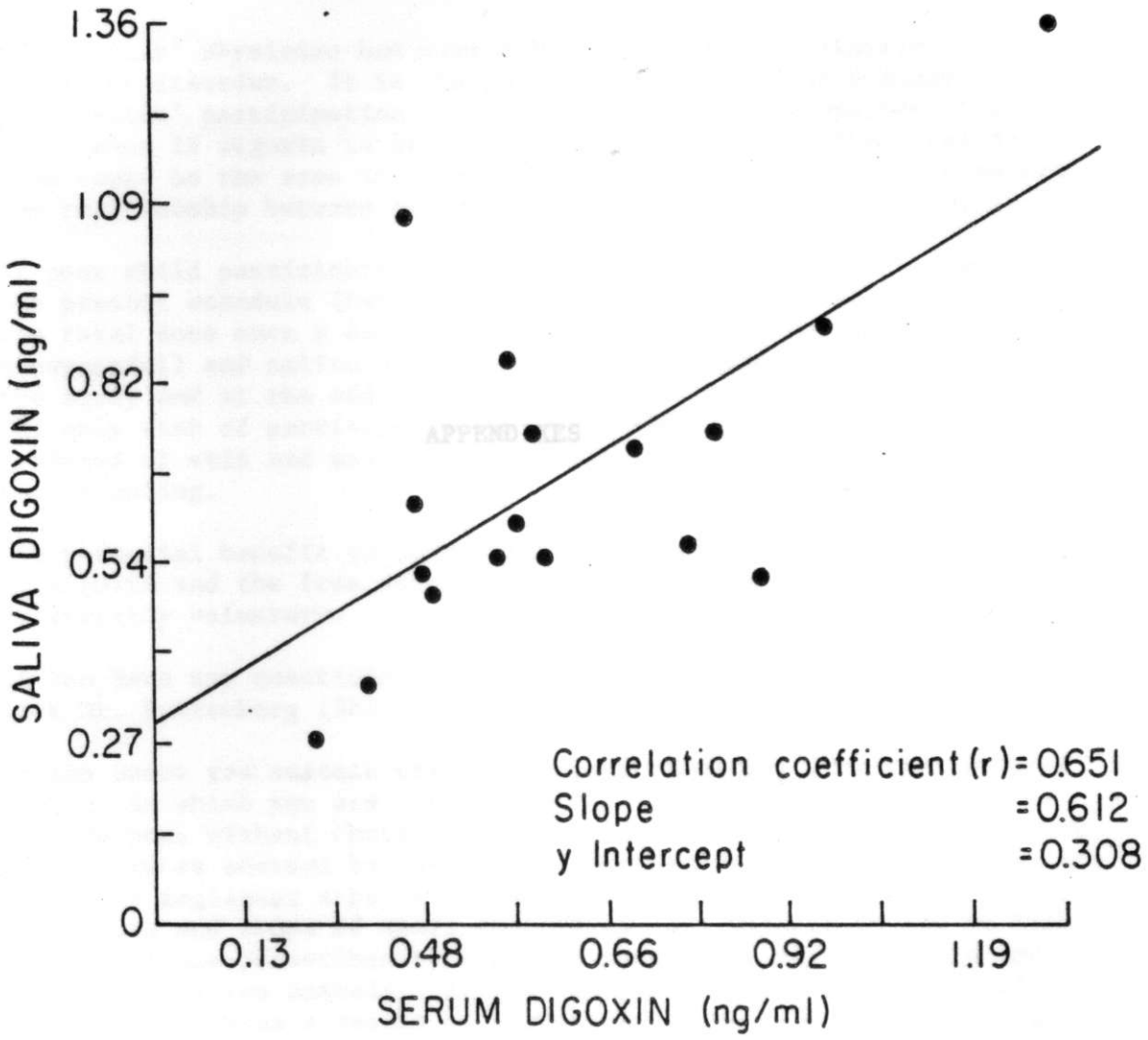


Figure 2. RELATIONSHIP BETWEEN SALIVA AND SERUM DIGOXIN



APPENDIXES

APPENDIX A

COMPARISON OF ONCE VS TWICE A DAY DIGOXIN DOSING

Consent and agreement to participate as an experimental research subject in clinical research.

Date_____

Your childs' physician has prescribed a drug called digoxin for his or her heart disorder. It is the purpose of this research study, in which your childs' participation is invited, to determine whether it makes a difference if digoxin is given once or twice daily. The total daily dose would be the same in either case. We are also trying to determine the relationship between blood and salivary levels of digoxin.

If your child participates he or she will continue to take digoxin on the present schedule (twice a day) for two weeks and will then take the total dose once a day for two weeks. Blood (less than one-half teaspoonful) and saliva samples will be collected on the first day of the study and at the end of each two week interval described above. The only risk of participation in this study is that of drawing blood (redness of vein and mild pain). There is no financial cost for participating.

The potential benefit to your child is a simplified dosing schedule of digoxin and the free determination of digoxin levels. Participation is strictly voluntary.

If you have any questions during the course of this study you may contact Dr. Ruttenberg (581-7340) or Dr. Bosso (581-7545).

In the event you sustain physical injury resulting from the research project in which you are participating, the University of Utah will provide you, without charge, emergency and temporary medical treatment not otherwise covered by insurance. Furthermore, if your injuries are caused by negligent acts or omissions of University employees acting in the course and scope of their employment, the University may be liable to limitations prescribed by law, for additional medical costs and other damages you sustain. If you believe that you have suffered a physical injury as a result of participating in this research program, please contact the Office of Research Administration, phone number 581-6903.

I acknowledge that I have had a fair opportunity to ask questions about the above procedures. I understand that I am free to withdraw my consent and to discontinue my child's participation in the project at any time without prejudice. I agree that data from these experiments may be used for medical and scientific purposes, including publications, with understanding that my child's identity will not be revealed unless I expressly consent thereto.

Patient Name:_____

Signature of Parent or Legal Guardian:_____

Witness:_____

APPENDIX B

Patient's Daily Record

Date Began:_____

Time of Dose

Date	A.M.	P.M.	Comments

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Doctor of Pharmacy
University of Utah
Salt Lake City, UT
1981-1983

Residency in Clinical Pharmacy Practice
University of Utah
Salt Lake City, UT
1981-1983

UNIVERSITY HONORS

Hebrew University, School of Pharmacy, Jerusalem, Israel
1971-1974

TRAINING FELLOWSHIP

Hadassah Hospital
Jerusalem, Israel - 1981

Fund for Higher Education
Tel Aviv, Israel - 1981

American Association of University Women Educational Foundation
Washington, DC - 1982

TEACHING EXPERIENCE

Teaching Assistant
Physical Pharmacy for Third Year Pharmacy Students
Hebrew University School of Pharmacy
Jerusalem, Israel
Autumn 1976, 1977

Teaching Assistant
Pharmaceutics for Second Year Pharmacy Students
Hebrew University School of Pharmacy
Jerusalem, Israel
Spring 1977, 1978

Teaching Fellow
Adult Medicine, Pediatrics, Obstetrics and Gynecology, Drug Information, Ambulatory Care, Surgery, and Geriatric Clerkships
Department of Pharmcy Practice
College of Pharmacy
University of Utah
Fall 1981 - Spring 1983

Responsibilities: Teach skills in patient monitoring, drug therapy selection, medication histories, and conduct pharmacy rounds

PROFESSIONAL EXPERIENCE

Pharmacy Intern
Norsk Medicinal Depot
Oslo, Norway
June 1975 - December 1975

Responsibilities: Compounding and dispensing of medications, production and quality control under the supervision of a registered pharmacist

PROFESSIONAL EXPERIENCE (continued)

Registered Pharmacist
State Support Health Maintenance Organization
Jerusalem, Israel
January 1976 - June 1976

Responsibilities: Compounding and dispensing of medications, patient counseling

Research Assistant
School of Pharmacy
Jerusalem, Israel
July 1976 - December 1976

Responsibilities: Laboratory technician, improving a micro-encapsulation project

Practical Nurse
Surgery
Hadassah Hospital
Jerusalem, Israel
July 1977 - June 1978

Responsibilities: Pre and postsurgery patient care which included administering medication (oral and intravenous), dressing changes, etc.

Clinical Pharmacist
Hematology/Oncology
Hadassah Hospital
Jerusalem, Israel
July 1978 - June 1981

Responsibilities: Patient drug histories, counseling, monitoring adverse drug reactions, chemotherapy admixtures, inservices to nurses and medical staff, Journal Club

Clinical Pharmacy Resident
Department of Pharmacy Practice
University Hospital
University of Utah
August 1981 - June 1983

Adult Internal Medicine	18 weeks
Ambulatory Care - Geriatrics	12 weeks
General Pediatrics	6 weeks
General Surgery	6 weeks
Adult Infectious Disease	6 weeks
Adult Cardiology	6 weeks

PROFESSIONAL EXPERIENCE (continued)

Drug Information . . . . . 6 weeks
Obstetrics and Gynecology . . . . . 6 weeks
Psychiatry . . . . . 6 weeks
Hospital Pharmacy Management . . . . . 3 weeks
Burn Unit . . . . . 3 weeks
Pediatrics Hematology/Oncology . . . . 3 weeks
Pediatrics Neurology . . . . . 3 weeks

(Medical team member, daily patient care rounds, monitoring patient therapy, performing medication histories, providing pharmacokinetic and drug therapy selection, inservice presentations, and pharmacy rounds)

On-call clinical pharmacy (Drug Information Service, Toxicology Service, Cardiac Arrest Team)

Clinical Pharmacy Seminars (to faculty members and hospital pharmacists at the University of Utah)

Committee meetings (Institutional Review Board, Pharmacy and Therapeutics Committee)

Research (see Research in Progress)

RESEARCH AND OTHER CREATIVE WORK

Principal Investigator: Clinical Pharmacists' Role in Improving Patient Compliance. Shimona Yoselsson-Superstine, Pharm.D., Michael Levy, M.D., October 1976-January 1978.

Co-Investigator: A Comparative Analysis of Plasma Concentration in Once-a-Day VS Twice-a-Day Digoxin Regimen in the Pediatric Patient. John A. Bosso, Pharm.D., Herbert Ruttenberg, M.D. - Funded by Burroughs Wellcome - $900. March 1982-present.

ARTICLES IN REFEREED JOURNAL

Yoselsson-Superstine S, Klieman R, Levy M: Clinical pharmacist's role in improving patient compliance. J Clin Pharm 1979; 4:53-57.

MISCELLANEOUS PUBLICATIONS

Klieman R: Transcutaneous nitroglycerin patches. Drugs in Patient Care (University of Utah Hospital) 1982; 5:6.

Klieman R: Timolol: a non-selective beta-blocker for reducing mortality following myocardial infarction. Drugs in Patient Care 1982; 5:7.

INVITED PRESENTATIONS

"Amiodorone - A New Antiarrhythmic Agent" Presented to medical housestaff, University of Utah Medical Center, Salt Lake City, UT, May 1982.

"Amrinone - A New Inotropic Agent" Presented to medical housestaff, University of Utah Medical Center, Salt Lake City, UT, May 1982.

"Renal Tubular Acidosis" Presented to medical housestaff, University of Utah Medical Center, Salt Lake City, UT, May 1982.

INVITED LECTURES

"Management of Pulmonary Tuberculosis" Presented to first year Doctor of Pharmacy Candidates, in Advanced Pharmacotherapeutics Course, College of Pharmacy, University of Utah, January 1983.

"Management of Chronic Renal Failure" Presented to first year Doctor of Pharmacy Candidates, in Advanced Pharmacotherapeutics Course, College of Pharmacy, University of Utah, January 1983.

PROFESSIONAL SOCIETY MEMBERSHIPS

Israeli Society of Pharmacists
January 1976 - June 1981