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THE BIOAVAILABILITY AND PHARMACOKINETIC BEHAVIOR OF DIGITOXIN

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ABSTRACT

The bioavailability and pharmacokinetic behavior of digitoxin, given intravenously, intramuscularly, in oral solution, and in three tablet forms, was studied in normal volunteer subjects. Bioavailability was evaluated by comparison of areas under the serum concentration curve and also by computation of the initial condition in the absorptive compartment at time zero. The bioavailability of oral digitoxin was found not to be complete. That of the oral solution was 93%. Tablets of 0.1,0.15, and 0.2 mg were respectively 78, 75, and 71 percent bioavailable. Pharmacokinetic analyses evaluated models with both 1 and 2 peripheral compartments. The first model had V = 6862.3 ml (102 ml/kg), Kel = 0.906 $days^{-1}$, Kcp= 30.78 $days^{-1}$, and Kpc =8.488 $days^{-1}$ The Ka was 27.63 $days^{-1}$ for the oral solution, and averaged 14.6 $days^{-1}$ for the 3 tablet forms. The pharmacokinetic model thus developed appears to have clinical relevance.

INTRODUCTION

It has generally been thought that the bioavailability of oral digitoxin is essentially complete. However, because of the demonstrated variability of uptake found from various formulations of oral digoxin, which led to much regulatory action by the FDA (1-7), it was decided to examine, in normal volunteer subjects, the bioavailability of an oral solution of digitoxin and to compare that bioavailability with that of three different sizes of digitoxin tablets and with intravenous and intramuscular administration of digitoxin. In addition, the pharmacokinetic behavior of digitoxin was evaluated.

METHODS

The original aim of the study was to evaluate the bioavailability of digitoxin by comparison of the areas under the serum concentration curves for each route or mode of therapy. The study employed an open-label 3-way crossover design, utilizing a randomized treatment order in which each subject was scheduled in a random manner to receive 3 out of 5 possible modes of treatment. These modes were:

1. An oral solution of 0.6 mg of USP Digitoxin in 200ml of 2% ethanol, thus containing 3 mcg per ml).

2. Six tablets of USP Digitoxin of 0.1 mg each (Lot # P38891).

3. Four tablets of USP Digitoxin of 0.15mg each (Lot # P38893).

4. Three tablets of USP Digitoxin of 0.2 mg each (Lot#P38756) .

5. An intravenous (IV) infusion of 0.6 mg of USP Digitoxin, given over a 15 minute period. (0.6 mg of the IV-IM preparation was diluted

to a total volume of 50 ml with sterile normal saline solution).

6. In addition, selected subjects also received an intramuscular (IM) injection of0.6 mg of digitoxin(Lot #6WE02A). A11 preparations of digitoxin were generously supplied by the Eli Lilly Company.

The study was approved by the Institutional Review Board of the USC School of Medicine and the LAC/USC Medical Center. Subjects were chosen from medical students of the USC School of Medicine and from the staff of the Los Angeles County/USC Medical Center. Each volunteer entered the Clinical Research Center (CRC) of the LAC/USC Medical Center on the afternoon before the study, and gave his/her informed written consent. A thorough history, physical examination, electrocardiogram, and chest x-ray were performed. Height and weight were recorded. Blood was obtained for hemoglobin, hematocrit, red and white cell counts, differential, blood urea nitrogen, alkaline phosphatase, bilirubin, CPK, SGOT, SGPT, fasting blood sugar, creatinine, sodium, potassium, C02 / chloride, calcium, phosphorous, total serum protein, albumin, globulin, cholesterol, uric acid, and prothrombin time. A low-fat diet was given. The patients originally were fasting from midnight until lunch time. This was subsequently modified (see Results) so that they received a snack of juice and crackers at10:30AM, 2 hours after receiving the drug at8:30AM. A low-fat lunch was given at12:30 PM.

All subjects were confirmed to be essentially normal healthy persons. All were free of significant cardiovascular, gastrointestinal, hepatic, renal, or respiratory disease.

The electrocardiogram was monitored throughout the study day. Blood samples for serum digitoxin concentrations and an EKG rhythm strip were obtained just prior to administration of the drug,

and (for IV administration only) at 15 minutes (the end of the intravenous infusion, from the other arm). Further serum samples and rhythm strips were obtained at 20, 30, 40, 60, 90 minutes, and at 2, 3, 4, 6, and 8 hours afterward. The subject then went home, but returned for a blood sample daily for the next 13 days. Urinary and fecal excretion of the drug were not studied.

Following this, a rest period of at least 4 weeks took place. The subject then returned for his/her 2nd study, which was done with an identical protocol and rest period, and then for the 3rd study, also done with the same protocol.

Some subjects also consented to return, after a similar rest period, for a 4th study, receiving the drug by the intramuscular route. An identical study protocol was again followed.

Pharmacokinetic analyses and evaluation of areas under serum concentration curves were done using the ADAPT collection of computer programs for simulation and parameter identification (8). Body surface area was computed by the formula of Gehan and George (9). Ideal (non-obese) body weight was calculated from the algorithm of 100 lb for the first 5 feet of height, plus 5 lb for each additional inch over 5 feet, plus 10 lb for a male or 5 lb for a female subject (10). Differences in goodness of fit were evaluated by the F ratio test (11). Difference between population means were evaluated by the T test for small samples (12).

Determination of digitoxin in the serum samples was performed by radioimmunoassay according to the method of Besch and Watanabe (13) with the following modifications:

1. A standard curve was made up in the zero-hour serum sample for each subject for each set of samples. This served to minimize the

effects of variable amounts of protein-binding on the shape of the standard curves.

2. A set of control standards, made up in pooled serum, was also run during each test in order to compare long-term drift in the results. The overall co-efficient of variation for these "master" curves was 6.5% at 14 ng/ml, and 11.4% at 2 ng/ml.

The assay results were calculated by Burger's computer program (14) after correction of the tritium counts by the external standard ratio method. The limit of detection was 0.5 ng/ml (two standard deviations from the zero-level counts). Individual assays had an average coefficient of variation of + 2.8% between the range of 7.6 - 46.3 ng/ml. These individual curves varied in shape from the master standard curves and from each other, thus justifying the use of each subject's control serum as the medium for his own standard curve.

RESULTS

The randomized treatment matrix for 20 patients was begun. During the study, 3 subjects dropped out after receiving the first treatment mode of the study. One female subject, who received the 0.1 mg tablets, developed a vasovagal reaction with syncope and sinus bradycardia (rate 45-50 min) at 11:30AM, 3 hours after receiving her dose. A blood sugar was not low at the time. After that episode, however, a small snack was given to all subjects at 10:30AM. No other patient had any similar episodes. Another female subject, who received the oral solution, developed mental confusion the evening of the study, and was readmitted to the CRC. No arrhythmia was noted at any time. She was reassured, left the CRC the next day, and did well thereafter. Both the episode of

mental confusion as well as the vasovagal episode were felt to represent possible evidence of digitalis toxicity, probably in combination with other factors. In addition, 3 female subjects stated that their menstrual periods might possibly have been transiently altered by the study, but this was impossible to document as anything more than a vague impression.

When additional subjects were added to the study, the original matrix of treatment modes was partly repeated, in an attempt to have a total of at least 20 subjects in the study.

A group of 22 subjects, 11 men and 11 women, was finally obtained. Their ages averaged 31.6 years and ranged from 2 4 to 57 years. The male subjects averaged 28.9 years, the females 34.5 years. No significant difference in age was present between males and females ($t = 1.328$, $DF = 20$, $P = NS$).

Within this group of 22 subjects, 11 received digitoxin by the 15 minute intravenous infusion, 11 received the oral solution, 13 received the six 0.1 mg tablets, 15 received the four 0.15 mg tablets, and 16 received the three 0.2 mg tablets. Five subjects also received it by the intramuscular route, which was frequently very painful for several hours.

Figure 1 shows the average of the serum concentrations found in all subjects from each mode of dosage. The two parenteral forms of therapy generally had the highest serum concentrations. The average peak after intramuscular administration was reached 3 hours after the dose, and, though slightly higher, was only slightly different from the peak times of 2 or 3 hours found with the various tablet forms.

In contrast, the peak following the oral solution was reached much earlier, at 30 minutes, and was much higher (almost 42 ng/ml) than the IM and tablet forms, which were only about half that high at their peaks.

Three hours after the dose, however, all serum concentrations were quite similar, though those from the 2 parenteral forms usually were slightly higher. The concentrations found with the oral solution and the 3 tablet forms were similar after 3 hours. Thus, no evidence was found to suggest any "sequestration" of IM digitoxin.

EVALUATION OF BIOAVAILABILITY BY AREA UNDER THE SERUM CONCENTRATION CURVES

The averaged serum concentrations from IM, IV, oral solution, and from the 0.1, 0.15, and0.2 mg tablets yielded areas (trapezoidal rule) of 111.7, 97.7, 79.7, 78.3, 78.2, and 77.3 ng-days/ml respectively. Thus the areas from the IM, IV, oral solution,0.1mg tablets,0.15 mg tablets, and the0.2 mg tablets were respectively 114.3%, 100%, 81.5%, 80.1%, 80.0%, and 79.1% of the area found with the IV route. This unadjusted averaged data suggests that the oral solution was about 82% bioavailable, and that the tablet forms were about 80% bioavailable.

However, since not all the same subjects received the various dosage forms, it was decided to determine the area under each individual subject's serum concentrations, to find the mean and standard deviation of that area for all such subjects in each group, and to test whether or not a significant difference was present between any of the groups. In Table 1, the top two rows show that the average of the areas under the serum concentrations

of subjects receiving the 0.1 mg and 0.2 mg tablet forms were

slightly but significantly (P just < .05) less than that found in the IV subjects. However, the subjects receiving the 0.1 mg tablets also had a slightly smaller average body weight (136.1 lb) than did the IV subjects (148.1 lb). Because of this, it seemed proper to evaluate the effect of body weight on the area under the serum curves by multiplying the area by the body weight and then normalizing it to 70 kg. Thus large subjects, who might have smaller areas, would be made more equal to smaller ones who would have larger areas.

The results of this evaluation are shown in Table 1, rows 3, 4, and 5 from top. As with the unadjusted areas, these weight adjusted areas also showed slightly but significantly smaller values in the subjects receiving the 0.1 and 0.2 mg tablet forms compared to the IV values.

The effect of ideal body weight (see Methods) upon the individual areas was next examined. The area under the serum curve was multiplied by the weight obtained with this algorithm for ideal body weight and again normalized to 70 kg. This was done because digitalis glycosides distribute poorly into body fat, making a non-obese type of weight perhaps more appropriate to the volume of the body into which digitalis glycosides are usually distributed.

The results of this analysis were most interesting. As shown in Table 1, rows 6, 7, and 8, from top, all tablet forms were now found to have significantly ($P < .05$) smaller adjusted areas than that of the IV route. The 0.1, 0.15, and 0.2 mg tablets had only 70.6, 72.5, and 73.5 percent of the adjusted IV area, while the oral solution achieved 78.6 percent.

Lastly, the effect of multiplying area under the serum curve by body surface area and normalizing to 1.73 square meters was examined. As shown in Table 1, bottom 3 rows, no further helpful information was obtained.

In summary, analysis of the various areas under the serum concentration curves showed that the oral solution achieved approximately 80 percent of the corresponding IV area, while the 0.1 mg, 0.15 mg, and 0.2 mg tablets achieved approximately 72, 75, and 75 percent respectively, when the percents with the 3 different types of adjusted areas were averaged.

PHARMACOKINETIC ANALYSES

The average serum levels for all the patients receiving the IV infusion were fitted in the manner described below, with

1) A model also having one peripheral compartment, as in Figure 2a, and

2) A similar model having two peripheral compartments, as shown in Figure 2b.

All data points were assigned equal weight in the fitting process. The parameter values found for a 1-compartment model were first obtained from a variety of initial values in the literature. The sole reason for finding these values of V and Kel for a 1-compartment model was to use them as the starting estimates for parameter identification for the 1st peripheral-compartment model. In the latter model, the initial estimates for the rate constants to and from the peripheral compartment ranged from 1.0 to 100 $days^{-1}$. Table 2 shows the values found for these parameters. A significant reduction of the sum of the squares of the differences was found from a 1-compartment model (F ratio = 143.46, DF = 2, 20, P <

0.0005).

The same data was then fitted to the model with 2 peripheral compartments. A further significant improvement in fit was noted (F ratio=19.13, DF =2, 18, P< 0.0005). While the Kel was virtually unaltered in this last model, the additional peripheral compartment resolved the distribution process into 2 separate groups, one faster and one slower, in their exchange with the central compartment.

If one should try to impute some physiological meaning underlying these figures, a process to be regarded with much skepticism, it is interesting that the apparent volume of the central compartment, V , is close to that of the vascular space, consistent with the high degree (approximately 95%) of binding of digitoxin to serum albumin. The apparent rate constant for elimination, Kel, was surprisingly fast, equivalent to a half-time of 20 hours. This is close to the reported half-time of ouabain, a glycoside which enters cells only to a small degree, if at all, and which thus may not have any significant distribution outside the extracellular fluid volume.

The data thus suggest that the elimination of digitoxin may be more rapid than previously thought, and that the slow terminal phase of decay seen with digitoxin may in fact be due to slow return to the central compartment from peripheral tissue depots.

CRITIQUE OF PHARMACOKINETIC RESULTS

One of the limitations of pharmacokinetic studies is that they may not be carried out long enough to obtain data to capture slow trends or long half-times. Similarly, serum concentration data from a single-dose study may sometimes decline rapidly to negligible values, thus preventing one from obtaining proper

values for the longer half-times often found in multiple-dose studies.

These questions were evaluated first by a visual inspection of the averaged serum data shown in Figure 1. It is noteworthy that if one ignores all serum data obtained earlier than 8 hours after the dose (during the distribution phase), a total of 14 later data points were still available for fitting, covering almost 2 weeks, about twice the reported terminal half-time of digitoxin. Furthermore, significant values were present at all data points. Inspection of Figure 1 shows serum concentrations of about 12 ng/ml at 1 day, falling to about 6 ng/ml at 6 days, and to just under 3 ng/ml at 11 days, suggesting that the terminal half-life of digitoxin in these normal volunteer subjects was about 5 days, close to the range of 6 days found for most cardiac patients with normal renal and hepatic function, who are usually somewhat older than the subjects in the present study.

These findings show that adequate long-term data was in fact present, and that it covered a period of somewhat more than twice the reported half-time of digitoxin. Because of this, the rapid Kel found for the 1 and 2-peripheral compartment models (see Table 2) appears valid.

While the averaged data of serum levels in the IV recipients was actually best fitted by the model having 2- peripheral compartments, the model having 1-peripheral compartment may be more useful clinically, for 3 reasons. First, when one actually looks at each individual subject's serum data, there was much scatter and noise, thus probably preventing any significant further improvement in fit that a model having 2-peripheral compartments might give. Second, at least 6 serum concentration values are

required to fit such a model, (6 parameter values must be found) while only 4 are needed to fit the model having only 1-peripheral compartment with only 4 parameter values to find. Third, analytic solutions can be employed for the less complex model, greatly reducing computing time and increasing the cost effectiveness.

EVALUATION OF BIOAVAILABILITY BY IDENTIFICATION OF THE INITIAL CONDITION IN THE ABSORPTIVE SITE.

Use of the parameter identification portions of the ADAPT collection also permits one to compute, just as one would any other parameter value, the apparent amount of drug present in the absorptive site at time zero, immediately after placing the dose in that compartment (8) This represents a direct estimate of the total effective dose having 100% bioavailability in the absorptive compartment. Computation of the initial condition in the absorptive site thus provides a new tool to evaluate the bioavailability of a drug. To our knowledge, this is the first instance in which this technique has been used to evaluate the bioavailability of a drug.

In this evaluation, the parameter values found with IV administration for the model having a 1-peripheral compartment were used as given in Table 2, and were held fixed. This prevented any possibility of the data being confounded by problems of structural identifiability (15). The averaged serum concentration data shown in Figure 1 from the IM route, from the oral solution, and from the 3 tablet forms were then each analyzed. V was adjusted for the small differences in non-obese body weight from the IV group (6658 ml) and thus was held fixed at 6499, 6632, 6023, 6247, and 6502 ml for the IM, oral solution, and the 0.1 mg, 0.15 mg, and0.2 mg tablet data respectively. Values for Kcp_1, Kpc_1, and Kel were held fixed at 30.4, 8.867, and 0.8235 $days^{-1}$ respectively. Thus the parameters to be identified were Ka, the apparent rate

constant for absorptive uptake, and ICA, the initial condition (effective amount of drug) in the absorptive compartment at time zero, which then is completely taken up by the system. The dose given, 0.6 mg or 600,000 ng, was placed in the absorptive compartment as the starting estimate of its initial condition. Various widely ranging starting estimates of Ka were also employed.

Using this approach, Table 3 shows the values found for Ka and ICA, as well as the percent bioavailability. The data in Table 3 show that the computation of bioavailability by the identification of ICA, the initial condition in the absorptive compartment at time zero, correlates well with the traditional method of computing and comparing the areas under the serum level curve. The similarities and differences of these two methods are summarized in Table 4. Thus bioavailability, that amount of drug which is actually available in the absorptive compartment for complete uptake into the body, is simply another pharmacokinetic parameter to be identified, and cannot be separated or held apart from all the other pharmacokinetic behavior of a drug.

The above results thus suggest that the oral solution of digitoxin was 82% bioavailable, that the 3 tablet forms were approximately 75% bioavailable, and thus had 75/82, or 91% of the bioavailability of the oral solution.

PHARMACOKINETIC ANALYSES OF INDIVIDUAL PATIENTS

The above analyses were based on the averaged serum concentrations found at each time in the various subjects. We also wished to analyze each patient's individual pharmacokinetic parameter values and to examine the mean and standard deviation of these parameter values for the group as a whole. This was done using the parameter values found for the one peripheral

compartment model described in Table 2 as the initial estimates in the fitting process. It was felt that there was enough scatter and noise in the data that a model with 2-peripheral compartments probably would not result in a significantly improved fit when each patient's data was individually fitted. This question, however, was not examined further because of the time and cost involved.

Each of the 11 patients receiving digitoxin intravenously thus had his individual pharmacokinetic parameter values analyzed. The individual values found for the 11 patients are given in Table 5, along with their means and standard deviations. They were generally similar to those shown in Table 2. Next, the initial condition in the absorptive compartment and the apparent rate constant for absorption were computed in the same 11 patients, employing the above individual parameter values found with IV administration and the serum levels found with administration by the various oral and IM routes. The starting estimate of the initial condition in the absorptive compartment was 0.6 mg (the dose given). Initial estimates of the apparent rate constant for absorption were the values given in Table 3.

The results are shown in Table 6. Significant variation was found in all patient groups, as shown by large standard deviations. The values of ICA and Ka differ somewhat from those obtained by using the averaged serum data, especially in the case of the oral solution, where the apparent bioavailability (ICA) was found to average 92.8 ± 38% compared to 82.3 ± 4.1% where the averaged values were used. For the 0.1 mg tablets the apparent bioavailability was 78.1% versus 73.9%. For the 0.15 mg tablets it was 75.0% versus 74.0%, and for the 0.2 mg tablets it was 71.5% versus 77.3%. In all cases,

however, the coefficient of variation was large, and there were no significant differences found between these two sets of figures.

The results in Table 6 probably represent the best overall figures for bioavailability which can be derived from this study. They indicate that the bioavailability of the oral solution and the 0.1, 0,15, and the 0.2 mg tablets respectively is 93, 78, 75, and 71%, while that found with the intramuscular route was 106%.

It is interesting that the tablet form having the greatest surface area available to aid dissolution (6 tablets of 0.1 mg each) had the highest apparent bioavailability, that the form with the next greatest surface area (4 tablets of 0.15) mg had the next, and that the form with the least surface area (3 tablets of 0.2 mg) had the smallest apparent bioavailability. A similar trend was found for Ka, where the 0.1 mg tablets had the largest value and the 0.2 mg tablets had the lowest.

SIMULATION OF LONGER-TERM CLINICAL EVENTS

The model having 1 peripheral compartment was then used to simulate conditions which might result from administration of a loading dose of 0.7 mg of digitoxin, given as tablets, followed by 0.1 mg per day for a total of 10 days. Probable serum levels were computed, as well as amounts in the peripheral compartment. An assumed 75% bioavailability of an oral digitoxin dose in tablet form was used. An assumed Ka of 14.62 days (the average of the values for Ka for the 3 tablet forms shown in Table 6) was employed, along with V, Kcp_l, Kpc_l, and Kel of 6862.3 ml, 20.78 days^{-1}, 8.488 days^{-1}, and .906 days^{-1} respectively, taken from Table 5.

As shown in Figure 3 (a and b), the results of this simulation reasonably approximate relevant clinical events which are

generally known to occur on such a therapeutic regimen, with morning levels, before each daily dose, of 13.7 ng/ml after day 1, just before the first maintenance dose, gradually falling to 11.7 ng/ml on day 10, just before the 10th maintenance dose. Peak serum levels are reached at 1.5 hours after the dose, and decrease gradually from 21.2 ng/ml 1.5 hours following the loading dose, to 14.7 ng/ml 1.4 hours after the 9th maintenance dose. In addition, the time course of the computed amount present in the peripheral (tissue) compartment closely approximates the time course of pharmacological effect of digitoxin upon ejection time index (16).

After the loading dose, the peak effect on ejection time index is shown to have a plateau extending from 6 to 24 hours (16). In the present model, the computed amounts in the peripheral compartment are 89% of peak at 4 hours, 97% of peak at 6 hours, 100% (peak) at 8 hours, 99% at 12 hours, 93% at 18 hours, and 89% at 24 hours after the loading dose. On subsequent days, the time to peak in the peripheral compartments shortens to 5 hours. Peripheral compartment amounts during the day of the 10th dose (the 9th maintenance dose) are 87% of peak just before the dose is given, rising to 95% of peak at 2 hours, 99% at 4 hours, 100% (peak) at 5 hours, falling to 99% at 8 hours, 95% at 12 hours, 89% at 18 hours, and 87% again at 24 hours after the dose. Thus the model, obtained here in a single-dose study, also simulates multiple dose clinical behavior reasonably well, both in terms of changes in peripheral compartment amounts correlating well with the time course of known inotropic effects of digitoxin, but also in terms of both computed serum concentrations and computed peripheral compartment amounts behaving in a simulation of loading and maintenance therapy in a manner not unlike serum concentrations commonly seen in patients on chronic therapy. Such correlations strongly suggest that the model having 1-peripheral compartment may well have clinical

relevance.

SUMMARY

A study of the bioavailability and pharmacokinetic behavior of digitoxin in normal volunteer subjects reveals that the oral solution studied had a bioavailability of about 93 percent. Tablets of 0.1 mg had a bioavailability of about 78 %, those of 0.15 mg had a bioavailability of about 75 %, and those of 0.2 mg had a bioavailability of about 72 %. The pharmacokinetic model developed in connection with this study appears to describe both the behavior of the central serum compartment appears to correlate well with the known behavior of the serum levels in patients. The behavior of the peripheral compartment appears to correlate well with the time course of the known inotropic effects of the drug. This model appears to have good potential for clinical use in planning, monitoring, and adjusting digitoxin therapy for patients, adjusted to their body weight and renal function.

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TABLE 1 - Average Individual Areas Under the Serum Level Curve, and those Areas Adjusted for Weight, Ideal Weight, and BSA.

	IM	IV Solution	O.lmg	0.15mg	0.2mg	Tablets
Avg Individual Area	106.4	98.9	81.5	78.3*	77.9	77.0*
% of IVArea	107.6	100	82.3	79.1	78.7	77.8
Avg Weight (lb)	148.0	148.1	151.5	136.1	145.3	152.3
Area times Weight/70kg	102.9	96.3	78.8	69.0*	72.8	73.9*
% of IV Area	106.8	100	81.8	71.8	75.6	76.8
Avg Ideal WT (lb)	141.0	144.5	137.4	130.8*	135.5	141.1
Area times Ideal WT/70kg	97.5	94.1	73.9	66.4*	68.2*	69.2*
% of IV Area	103.6	100	78.6	70.6	72.5	73.5
AVG BSA (M^2)	1.789	1.803	1.802	1.702	1.764	1.817
Area times BSA/l-73M^2	110.6	104.1	84.0	77.1*	79.1*	79.6*
% of IV Area	106.2	100	80.7	74.0	75.9	76.4

*P <.05 compared to that of IV route.

TABLE 2 - Fitted Parameter Values – IV Route

Parameter	1 Compt Model	1 Periph Compt Model	2 Periph compt Model
Kel (days-1)	10.8165	0.8235	0.8323
Kcp^1 (days-1)	0	30.402	32.313
Kpc^1 (days-1)	0	8.867	29.133
Ka	0	0	0
Kcp^2 (days-1)	0	0	12.373
Kpc^2 (days-1)	0	0	3.089
V_c (ml)	8626.2	6658.4	6096.4
Sum of Squares	1703.5	110.99 *	35.51**
Coefficient of Determination	0.915	0.990*	0.997**
Degrees of Freedom	22	20	18

- F = 143.46,, DF = 20, P < 0.005,compared to 1 compt model.

** F = 19.127, DF =2, 18, P<0.0005 compared to 1 periph compt model

TABLE 3 - Evaluation of Bioavailability by Identification of the Initial Condition (ICA) in the Absorptive Compartment.

Analysis	Ka, Ke, or both	ICA (mg)	% Bioavailability	CV% of ICA
Fixed Vc, Kel, Kcp1,Kpc1	Ka (days-1)			
IM	8.29	0.632	105.4	7.02
Oral soln	44.40	0.494	82.3	4.13
0.1mg tabs	11.67	0.444	73.9	5.89
0.15 mg tabs	9.93	0.444	74.0	6.28
0.2 mg tabs	9.12	0.464	77.3	7.18
Fixed Vc, Kel, Kcp1,Kpc1	Kel (days-1)			
IM	0.7605	0.624	104.0	5.42
Oral soln	0.8985	0.523	87.1	3.34
0.1mg tabs	0.8577	0.446	74.4	4.55
0.15 mg tabs	0.8068	0.443	73.8	4.86
0.2 mg tabs	0.8098	0.462	77.1	5.56
Fixed Vc, Kel, Kcp1,Kpc1	Ka	Kel (days-1)		
IM	8.72	0.411	0.611	101.8	9.30
Oral soln	43.59	0.9069	0.500	83.3	4.67
0.1mg tabs	11.51	0.8638	0.449	74.8	7.55
0.15 mg tabs	10.02	0.8018	0.441	73.5	8.21
0.2 mg tabs	9.19	0.8065	0.461	76.8	9.57
Average ICA and % Bioavailability					
IM			0.622	103.7	
Oral soln			0.505	84.2	
0.1mg tabs			0.446	74.4	
0.15 mg tabs			0.448	74.6	
0.2 mg tabs			0.463	77.1	

*CV = Coefficient of Variation (as percent of ICA found)

TABLE 4 - Comparison of Bioavailability Computed from Area and from Identification of the Initial Condition in the Absorptive Compartment.

	Oral Solution	IM	0.1 mg Tablets	0.15 mg Tablets	0.2 mg Tablets
% Bioavailability					
by Areas/SD	80.3/1.63	105.5/1.70	72.1/1.72	74.7/1.68	75.6/1.80
by ICA/SD	84.2/2.55	103.7/1.77	74.4/0.43	73.8/0.27	77.1/0.247
T	1.822	1.037	2.247	0.821	1.430
DF	4	4	2.249	2.08	2.07
P	NS	NS	NS	NS	NS

TABLE 5 - Pharmacokinetic Parameter Values Found in Individual Patients Receiving Intravenous Digitoxin

Patient	Vc (ml)	Kel (days-1)	Kcp(days-1)	Kpc(days-1)
1	4911.9	1.753	50.396	9.8454
2	7673.7	0.317	21.763	8.2962
3	5446.1	1.421	36.048	7.8166
4	6234.4	1.010	43.254	15.1920
5	9154.5	0.688	21.817	7.2916
6	7820.7	0.792	21.818	5.4073
7	6679.7	0.936	37.857	8.2436
8	4945.4	1.272	39.316	7.1379
9	7252.6	0.742	31.733	9.1361
10	8591.8	0.500	8.844	6.9034
11	6775.1	0.532	26.009	8.1017
Mean	6862.3	0.906	30.780	8.488
SD	1410.5	0.432	11.976	2.513

TABLE 6 - Computation of Ka and ICA in Individual Patients Who First Received IV Digitoxin.

Route	Patient	Ka(days-1)	ICA(ng)	Bioavailability
Oral Solution	3	14.99	892340	
	6	21.25	496660	
	7	11.24	631690	
	8	45.56	363620	
	11	45.12	399780	
	Mean	27.63	556818	
	SD	16.56	214551	92.8%
0.1 mg Tabs	4	17.76	343080	
	5	18.61	520350	
	10	24.86	508340	
	11	10.42	503330	
	Mean	17.91	468775	
	SD	5.91	84110	78.1%
0.15 mg Tabs	1	2.34	636370	
	2	26.09	412470	
	3	7.60	449970	
	4	7.24	355690	
	5	14.31	408370	
	8	18.06	421460	
	9	16.65	463970	
	Mean	13.18	449757	
	SD	8.04	89237	75.0%
0.2 mg Tabs	1	6.99	440060	
	2	9.41	337230	
	6	14.40	542980	
	7	8.00	566970	
	8	13.76	474040	
	9	7.85	368680	
	10	29.02	271620	
	Mean	12.78	428797	
	SD	7.74	108786	71.5%
IM	1	7.82	894240	
	2	2.21	377790	
	Mean	5.01	636015	
	SD	3.97	365185	106.0%

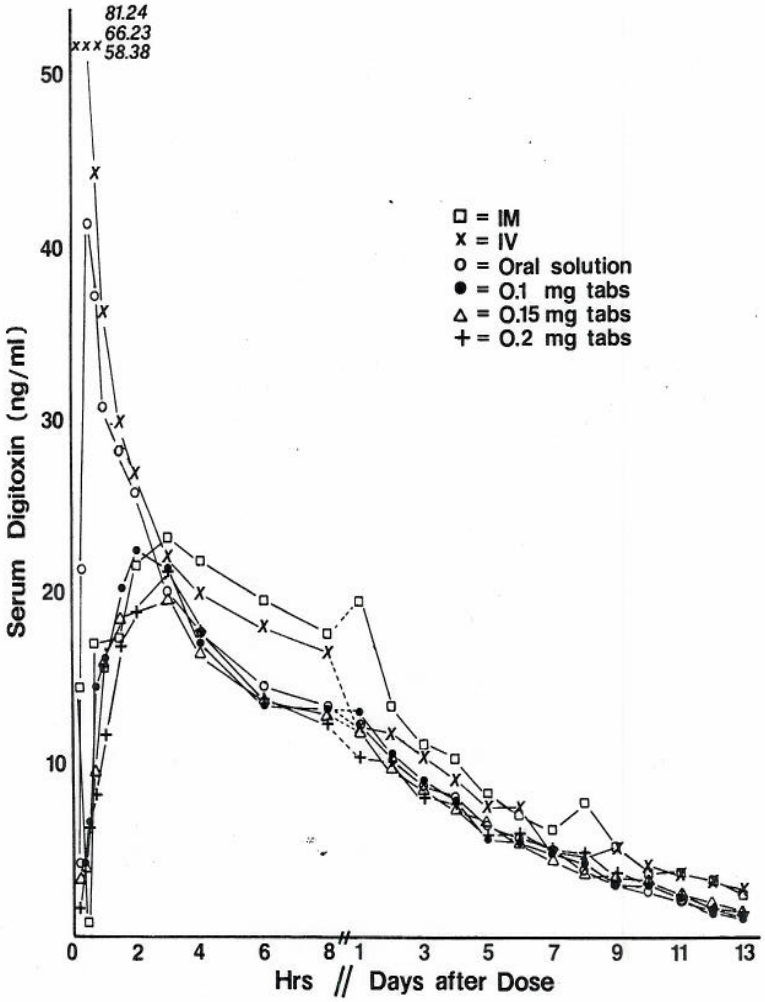
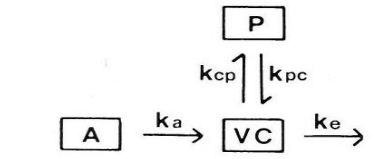
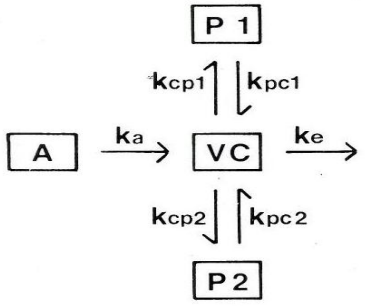


Fig.1 - Serum digitoxin concentrations found after a single dose of 0.6 mg given intramuscularly (IM), intravenously (IV), as an oral solution, and as 3 tablet forms. Each data point represents the average serum concentration found for all patients in each group at that time.



Absorptive Model with
One Peripheral Compartment



Absorptive Model with
Two Peripheral Compartments

Fig.2 - Block diagrams of the pharmacokinetic models of digitoxin evaluated in this study.

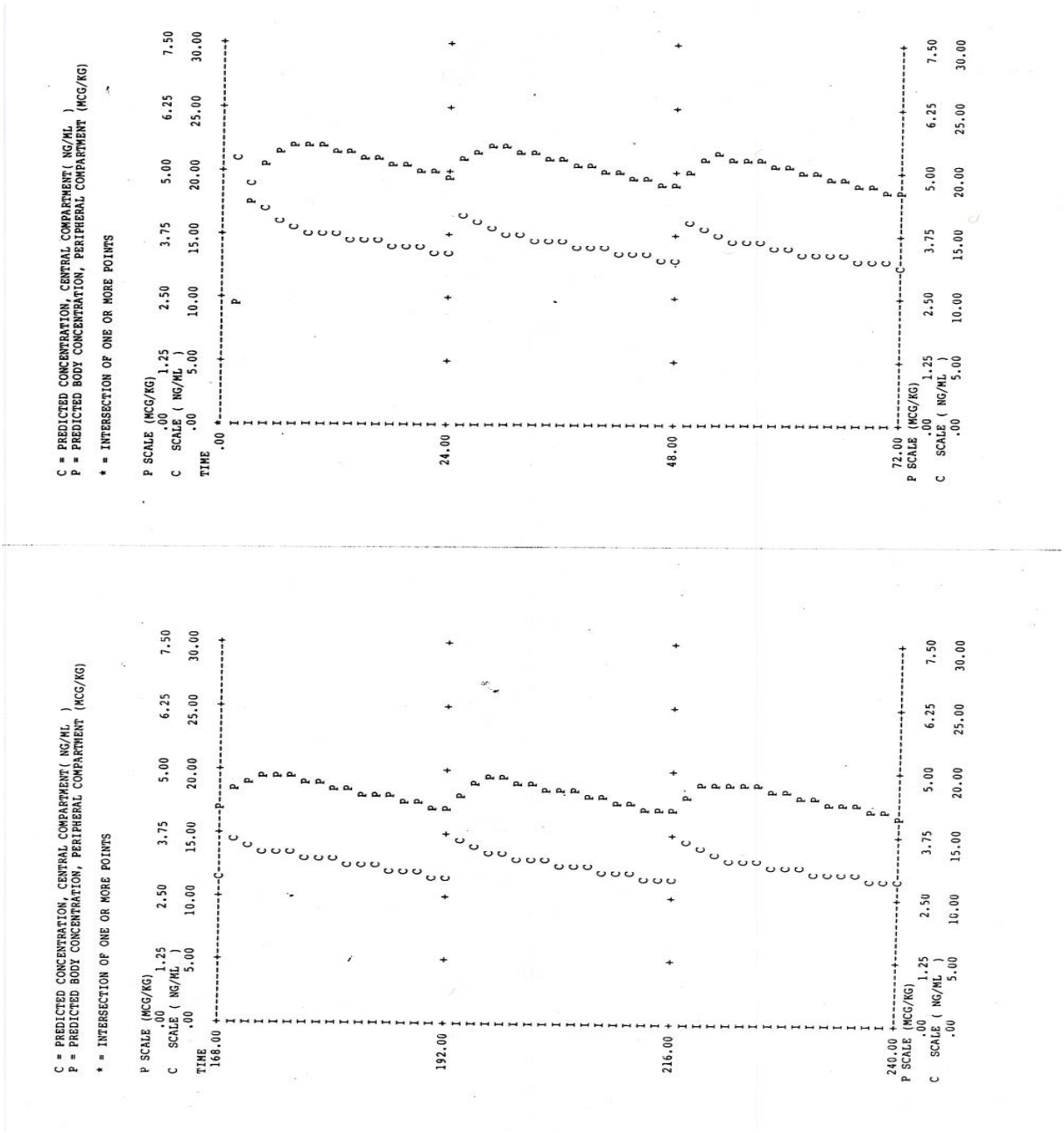


Fig.3 - Plot of predicted central compartment (serum) concentrations (ng/ml) and peripheral(total body) concentrations (mcg/kg) of digitoxin found using the 1-peripheral-compartment model. A simulated loading dose of 0.7 mg was given to the model, followed by 0.1 mg daily thereafter. P = Peripheral compartment predictions. C = Central compartment (serum) predictions. Vertical = Scales for P (mcg/kg) and C (ng/ml). Horizontal = Time (hrs into the regimen) plotted downwards from the top. Fig. 3a. - Plot of the first 3 days of the regimen. Fig. 3b. - Plot of the last 3 days.