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Pharmacokinetics of β-Methyldigoxin in Healthy Humans II: Oral Studies and Bioavailability

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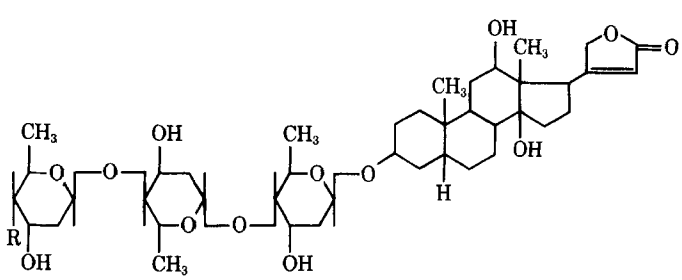
Abstract □ The pharmacokinetics of orally administered aqueous ^{3}H-β-methyldigoxin solutions were studied at two dose levels, 0.3 and 0.6 mg, in healthy human subjects. The drug and its metabolites were specifically assayed in biological fluids and compared with results after intravenous doses to the same subjects. No significant dose dependency was observed. The apparent half-life of absorption was 16 ± 6 min (*SEM*). Digoxin was the only metabolite observed in the plasma and comprised 28.6 ± 3.7% of the dose in the urine. ^{3}H-β-Methyldigoxin, renally excreted unchanged, comprised 25.7 ± 1.7% (*SEM*). Water-soluble metabolites in the urine comprised 9.0 ± 1.8%. Fecal and urinary excretion accounted for 85% of the dose at 144 hr. The oral absorption of unchanged ^{3}H-β-methyldigoxin from solution was 59 ± 6% by area under the curve methods and 60 ± 4% by renal excretion. A total of 73% of the dose in the solution was absorbed as β-methyldigoxin and digoxin. First-pass metabolism prior to absorption was largely prehepatic and assignable to GI degradation; 21.9 ± 2.8% was degraded with 12.8 ± 4.0% to digoxin and 9.1 ± 4.0% to water-soluble metabolites. From 14 to 18% of the administered oral dose did not reach the systemic circulation. Analog computer fitting of plasma and urine levels of drug and digoxin was consistent with the first-pass premise with a delayed absorption of GI-generated digoxin and other metabolites. There were no significant differences between the oral absorption of a tablet formulation and the solution. Orally administered β-methyldigoxin solution delivered 97% cardioactivity as itself and digoxin with respect to an equivalent amount of intravenously administered digoxin. This value contrasts to the 140% delivered by intravenously administered β-methyldigoxin on the premise of pharmacodynamic equivalence of systemically appearing digoxin and β-methyldigoxin. Literature reports on the oral bioavailability of solutions and solid dosage forms of digoxin were critically reviewed, but no reliable comparison of the extent and reproducibility of oral absorption of cardioactive agents from administered digoxin or β-methyldigoxin could be made from the widely variable digoxin studies with nonspecific assays.

Keyphrases □ β-Methyldigoxin—oral, pharmacokinetics and bioavailability in humans, radiochemical–TLC study □ Pharmacokinetics—oral β-methyldigoxin, humans, radiochemical–TLC study □ Bioavailability—oral β-methyldigoxin, humans, radiochemical–TLC study □ Radiochemistry–TLC—study of pharmacokinetics and bioavailability of oral β-methyldigoxin in humans □ Cardiac glycosides—β-methyldigoxin, oral, pharmacokinetics and bioavailability in humans, radiochemical–TLC study

Semisynthetic derivatives of digoxin (Ia) such as β-methyldigoxin (Ib), a methyl ether of digoxin, and β-acetyldigoxin (Ic), an acetyl ester of digoxin, have been claimed to have higher intrinsic rate constants and efficiencies of absorption than digoxin in animals and in humans (1–14). Presumably, the rationale for their preferred usage is that a completely absorbed compound has the most consistent bioavailability in multiple dosage regimens. This is a valid approach, since glycosides have a narrow therapeutic range (15–18) and the occurrence of toxic manifestations in patients undergoing chronic therapy is 7–20% (19). Whereas β-acetyldigoxin was extensively metabolized or degraded before reaching the systemic circulation (20), β-methyldigoxin was claimed to



Ia: R = OH
Ib: R = OCH_3 Ic: R = $OCCH_3$

Table I—Parameters for Orally Administered β-Methyldigoxin Pharmacokinetics by Graphical Methods

Parameter	Subject A (66.3 kg, 169 cm, 1.76 m² surface area)		Subject B (71.3 kg, 179 cm, 1.89 m² surface area)		Subject C (67.4 kg, 166 cm, 1.75 m² surface area)		Average ± SD
D, dose, μg	284	604	271	588	278	621	
k_a, hr^{-1} [a]	3.0	13.9	4.6	2.6	0.92	3.8	4.8 ± 4.6
10^2 area/D, hr/liter po (iv) [b]	6.1 (14.6)	7.6 (18.5)	6.6 (8.9)	7.4 (10.3)	9.6 (16.8)	11.3 (16.4)	8.1 ± 2.0 (14.3 ± 3.8) [m]
Clearances, ml/min							
$(Cl_p^u)_{tot}$ [c]	113	90	173	178	99	99	125 ± 40 (125 ± 40) [m]
$(Cl_p^u)_r$ [d]	62	46	99	63	44	42	59 ± 22 (59 ± 17) [m]
$(Cl_p^u)_m$ [e]	51	44	74	115	55	57	66 ± 22 (66 ± 24) [m]
Percent of β-methyldigoxin dose, D, in urine from							
$10^2\ U_{\infty}^{BMD}/D$ [f]	26.7	24.6	37.3	29.0	24.0	26.3	28.0 ± 4.9 (46.9 ± 5.3) [m]
$10^2\ U_{144\ hr}^{BMD}/D$ [g]	23.7	22.9	33.8	27.1	22.9	23.7	25.7 ± 4.3 (43.2 ± 4.7) [m]
$10^2\ U_{144\ hr}^{DIG}/D$ [h]	29.1	28.4	45.3	24.1	18.6	26.2	28.6 ± 9.0 (31.7 ± 5.5) [m]
$10^2\ U_{144\ hr}^{H_2O}/D$ [i]	9.9	12.3	4.7	6.4	14.2	6.3	9.0 ± 3.8 (5.3 ± 1.9) [m]
Absorption efficiency from [j]:							
areas, f_1	0.42	0.41	0.74	0.72	0.57	0.69	0.59 ± 0.15
U_{∞}^{BMD}	0.61	0.55	0.68	0.63	0.47	0.65	0.60 ± 0.08
$U_{144\ hr}^{BMD}$	0.61	0.57	0.67	0.62	0.50	0.62	0.60 ± 0.06
$U_{144\ hr}^{DIG}$	0.79	0.93	1.32	0.84	0.56	1.15	0.92 ± 0.29
$U_{144\ hr}^{H_2O}$	1.7	2.1	1.2	1.3	4.2	0.75	1.9 ± 1.2
Recovery of administered radioactivity at 144 hr [k]:							
Fecal, %	14.3	38.8	19.3	24.6	32.5	20.6	25.9 ± 8.1 (11.8 ± 1.6) [m]
Fecal + urinary, %	74.4	97.2	92.1	76.3	88.2	81.1	84.9 ± 9.1 (85.8 ± 2.7) [m]
144-hr recovery of β-methyldigoxin dose, % [l]	82	102	103	82	89	76	89.0 ± 11.2 (91.8 ± 6.5) [m]

[a] Apparent first-order rate constant of absorption of β-methyldigoxin from method of residuals on oral administration. [b] Determined by graphical integration of the area in micrograms-hour per liter under plasma unbound β-methyldigoxin concentration–time curve; this area is divided by the administered dose in micrograms. The parenthetical values were from the intravenous studies (25). [c] Total clearance from f_1D/area under plasma unbound concentration–time plots, where f_1 is the absorption efficiency from the ratio of the areas per unit dose for oral to intravenous administration. [d] Renal clearance from slope of plots of renal elimination rates of β-methyldigoxin, $\Delta U/\Delta t$, against plasma concentrations of unbound drug. [e] Metabolic clearance from the difference of total and renal clearances, $(Cl_p^u)_{tot} - (Cl_p^u)_r$. [f] Calculated from the micrograms of β-methyldigoxin renally excreted at infinite time, U_{∞}^{BMD}, which was estimated from adding to the amount excreted at 144 hr the amount that would have been excreted for five more half-lives if the slope of the natural logarithm of the excretory rate, $\ln \Delta U/\Delta t$, against time was a constant, $-\gamma$. [g] Calculated from the micrograms of β-methyldigoxin renally excreted at 144 hr, $U_{144\ hr}^{BMD}$. [h] Calculated from the micrograms of β-methyldigoxin equivalent of the digoxin renally excreted at 144 hr, $U_{144\ hr}^{DIG}$. [i] Calculated from the micrograms of β-methyldigoxin equivalent of water-soluble metabolites renally excreted at 144 hr, $U_{144\ hr}^{H_2O}$. [j] Value from oral administration divided by pertinent value from intravenous administration (25) for each subject. [k] Percent of total radioactivity administered excreted by 144 hr by specified route(s). [l] Percent of dose of β-methyldigoxin excreted by 144 hr renally as unchanged drug, digoxin, and water-soluble metabolite plus fecal excretion. [m] Parenthetical values were obtained from intravenous studies (25).

have a higher absorption efficiency than digoxin and β-acetyldigoxin on intraduodenal application in guinea pigs (3) and absorption efficiencies of 75–100% in humans (4–10).

These conclusions were based on pharmacodynamic cardiovascular parameters (4–6, 10) and the total radioactivity in plasma and/or excreted in urine after oral and intravenous administration (7, 8). Both methods do not give the intrinsic bioavailability of β-methyldigoxin, since the contributions of digoxin activity or the production of active or labeled metabolites prior to absorption cannot be excluded. Radioimmunoassay is a highly sensitive assay for cardiac glycosides (21, 22) and is applicable for the assay of the sum of β-methyldigoxin and its derived metabolites in biological fluids (22–24). It suffers from the same limitations as total radioactivity.

The pharmacokinetics of intravenously administered ^{3}H-β-methyldigoxin and its derived metabolites were considered previously (25). The present studies were conducted with the same subjects to determine the time course and bioavailability of ^{3}H-β-methyldigoxin and its metabolites, analyzed separately, at two dosage levels after oral administration.

EXPERIMENTAL

Details of the materials and analytical procedures used and the general pharmacokinetic procedures and design were given previously (25). The assayed solutions of 0.30- and 0.60-mg doses of ^{3}H-β-methyldigoxin in 0.9% saline solution were administered orally to the subjects (25) by a syringe with immediate swallowing to avoid sublingual or buccal absorption. A 40-ml water rinse was swallowed immediately. Blood (6 ml) was taken within 10 sec at 0, 2.5, 5, 10, 15, 20, 30, 45, 60, and 90 min and at 2, 3, 5, 7, 9, 11, 15, 20, 24, 36, 48, 60, 72, 84, 96, 120, and 144 hr after the oral drug administration through the butterfly needle with syringes; procedures were as described previously (25). The urine was collected

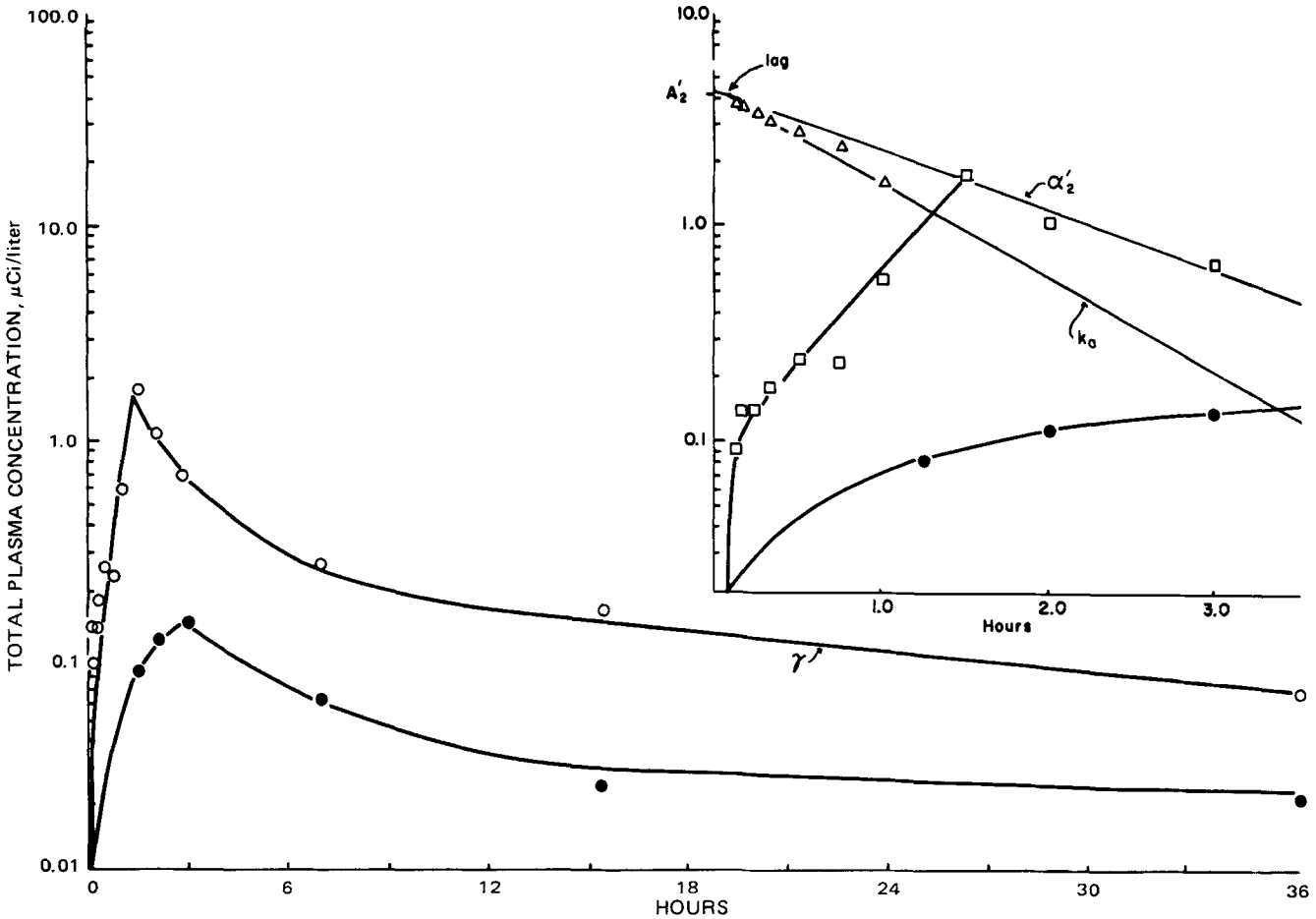


Figure 1—*Typical semilogarithmic plots of plasma β-methyldigoxin (○) and digoxin (●) concentrations, [A_p], against time for oral administration: 120.1 μCi = 278 μg of β-methyldigoxin in aqueous solution to Subject C. The insert is a plot of the plasma β-methyldigoxin (□) and digoxin (●) concentrations on an expanded time axis. The data were treated by the method of residuals by extrapolating the α_2-phase to time zero and plotting semilogarithmically the difference (△) of the antilogarithms of the extrapolated line and the plasma concentrations against time on the assumption that the absorption process was concluded during the α_2'-phase. The slope, $-k_a/2.303$, of this line permits estimation of the apparent first-order absorption rate constant, k_a. The lag time was estimated from the intersection of the extrapolated α_2-phase and the plot of the differences.*

and assayed as described in the intravenous studies (25). The subjects[1] were prostrate during the first 24 hr after drug administration.

In addition to the solutions, a tablet formulation of ^{3}H-β-methyldigoxin was administered to six of the seven volunteers. Five tablets (0.1 mg/tablet) with 100 ml of water were swallowed immediately, and biological fluids were sampled up to 24 hr after tablet administration as in the oral studies on solutions.

RESULTS AND DISCUSSION[2]

Plasma Pharmacokinetics of ^{3}H-β-Methyldigoxin after Oral Administration—The α_2-, β-, and γ-phases with pharmacokinetic constants similar to those of intravenous administration (25) were observed for ^{3}H-β-methyldigoxin. These phases were preceded by a rapid absorption phase, characterized by an apparent first-order absorption rate constant, k_a (Table I and Fig. 1). Peak plasma concentrations for total drug of 1.1 ±.0.1% of the dose/liter of plasma were reached at 50 ± 9 min after administration. The fact that these values were markedly consistent among doses, 1.14 ± 0.17 at 300 μg and 1.11 ± 0.15 at 600 μg (n = 3), was strongly indicative of a first-order absorption process. The rate constant, k_a, was obtained by "feathering" after excluding lag times of 9.4 ± 1.5 min. The α_2-phase of the semilogarithmic plot was extrapolated to zero time, and k_a was estimated from the linear slope of the differences of the antilogarithm of the extrapolated line and the plasma concentration against time (Fig. 1, insert) to give an apparent half-life of absorption of 16 ± 6 min.

The lack of dose dependency was evident by the superimposability of plots at various doses for the percent of dose per liter of plasma against time (Fig. 2).

Digoxin was the only metabolite observed in the plasma and peaked at 90 ± 24 min after oral administration of ^{3}H-β-methyldigoxin (Fig. 1), in contrast to the 32.3 ± 7.0 min observed after intravenous administration (25).

The apparent overall rate constant of elimination, γ, for the pseudo-steady state after equilibration among tissues, 19.3 ± 1.6 × 10^{-3} hr^{-1}, obtained from the slope of the semilogarithmic plot of plasma ^{3}H-β-methyldigoxin concentration against time, was not significantly different from the 17.3 ± 0.8 × 10^{-3} hr^{-1} value obtained after intravenous administration (25).

Urine Pharmacokinetics—The amounts of β-methyldigoxin cumulatively excreted in urine were plotted as percent of dose against time (Fig. 2) to estimate the total recovery and were reasonably superimposable for all doses. The apparent rate constant, γ, for the terminal phase of drug elimination in the urine, 20.5 ± 0.6 × 10^{-3} hr^{-1}, obtained from the slope of the natural logarithm of the amount yet to be excreted, $\ln(U_\infty - U)$ against time, was not significantly different from the 20.8 ± 0.5 × 10^{-3} hr^{-1} value obtained after intravenous administration (25).

The percentages of the ^{3}H-β-methyldigoxin dose renally excreted by 144 hr as β-methyldigoxin, digoxin, and water-soluble metabolites were 25.7 ± 1.7, 28.6 ± 3.7, and 9.0 ± 1.8 (Table I), respectively, in contrast to the intravenous values of 43.2 ± 1.9, 31.7 ± 2.2, and 5.3 ± 0.8, respectively (25).

The water-soluble metabolites in an 18-hr urine collection after oral administration were composed of glucuronides (42.4 ± 14.2%), sulfates

[1] Informed consent was obtained from all subjects. The protocol was approved by the Committee for Protection of Human Subjects and the Clinical Research Committee, J. Hillis Miller Health Center, University of Florida.

[2] The plus and minus values for mean values given in the text refer to the standard error, $\sigma/\sqrt{n}$, of such means, where σ is the standard deviation given in the tables of this paper or Ref. 25, and n is the number of values considered (6 unless otherwise specified).

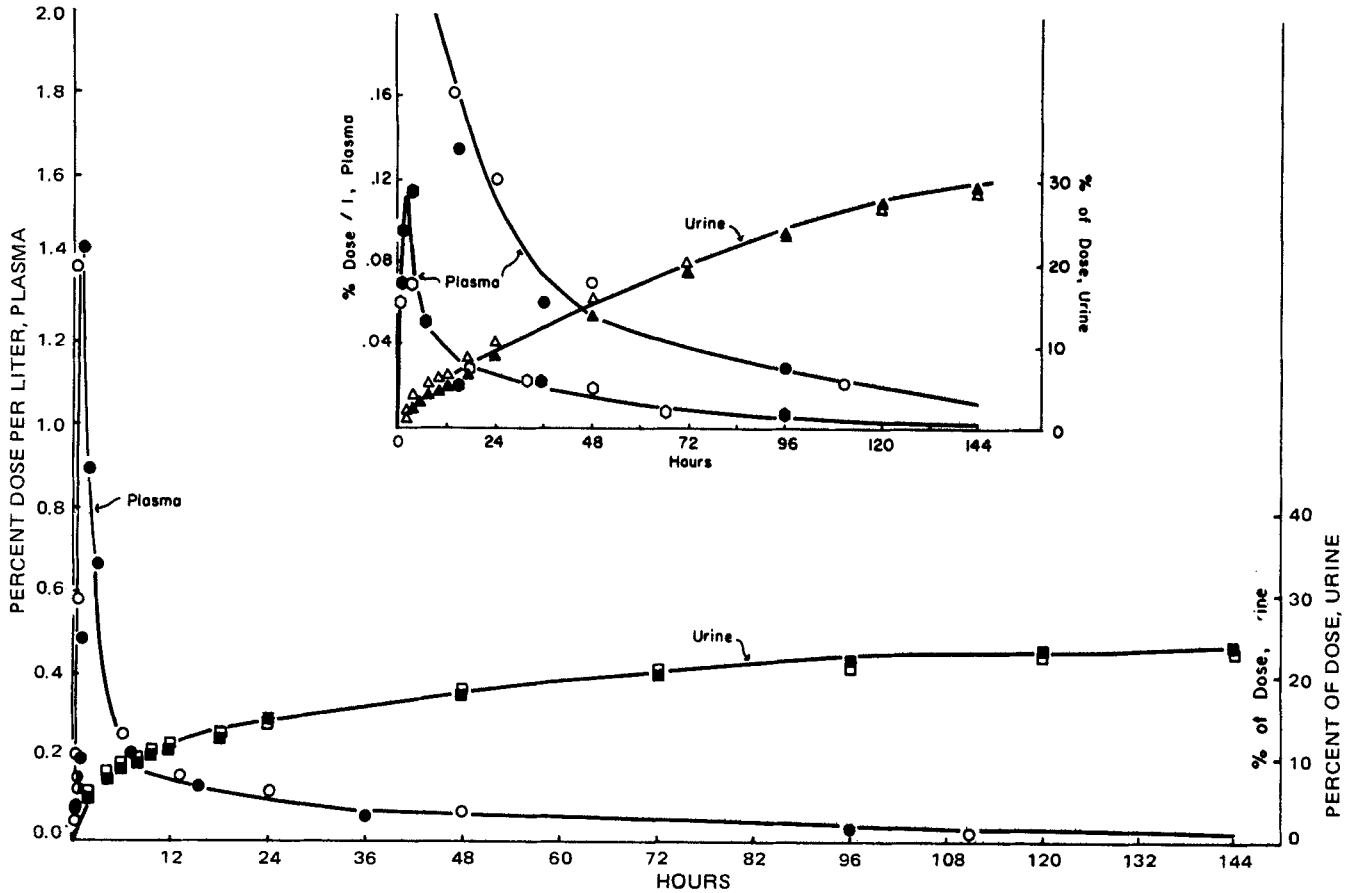


Figure 2—*Typical plasma concentrations and cumulative urine excretions in percent of β-methyldigoxin dose per liter of plasma and of dose, respectively, against time for oral solution administration: 126.7 μCi = 294 μg (open symbols) and 254.1 μCi = 590 μg (solid symbols) of β-methyldigoxin to Subject A. Key: ○, ●, plasma β-methyldigoxin levels; □, ■, urinary β-methyldigoxin amounts; ○, ● (inset), plasma digoxin levels; and △, ▲ (inset), urinary digoxin amounts.*

(24.6 ± 8.2%), and unidentifiable metabolites (33.6 ± 7.6%) (all $n = 3$). The percent compositions of these two fractions of glucuronide and sulfate conjugates were 82.4 ± 2.8 and 67.3 ± 9.8% with β-methyldigoxin, respectively, 8.6 ± 2.5 and 23.3 ± 9.6% with digoxin, respectively, and 9.0 ± 6.5 and 9.5 ± 1.2% with digoxigenin, respectively (all $n = 3$).

The percentages of the administered total radioactivity renally excreted as total radioactivity at 144 hr were 70.3 ± 1.2%, intravenous (25), and 57.7 ± 1.7%, oral ($n = 14$). The percentages of the administered total radioactivity fecally excreted as total radioactivity at 144 hr were 11.8 ± 0.6%, intravenous (25), and 25.9 ± 3.3%, oral. The combined urinary and fecally recovered amounts of total radioactivity at 144 hr were 85.8 ± 1.1%, intravenous (25), and 84.9 ± 3.%, oral, of the total radioactivity administered.

Clearances—The total clearances of unbound ^{3}H-β-methyldigoxin were calculated from:

$$(Cl_p{}^u)_{tot} = fD_{po}/area_{po} \qquad \text{(Eq. 1)}$$

where D_{po} is the orally administered dose. The area was determined under the plasma unbound concentration–time curves extrapolated to infinite time; f, the fraction of dose absorbed, was calculated from:

$$f = \frac{area_{po}}{D_{po}} \Big/ \frac{area_{iv}}{D_{iv}} \qquad \text{(Eq. 2)}$$

The areas and dose, D_{iv}, after intravenous administration to the same individual were given previously (25). Total clearance does not necessarily imply pharmacodynamic inactivation, since it includes the metabolic clearance of β-methyldigoxin where pharmacodynamically active digoxin is the major metabolite.

The total clearances of unbound β-methyldigoxin were the same after oral administration (Table I) as after intravenous administration (25). The average renal (59 ± 9 ml/min) and metabolic (66 ± 9 ml/min) clearances after oral administration were the same as those after intravenous administration, 59 ± 7 and 66 ± 10 ml/min, respectively (25). All clearances for a given individual were similar, whatever the mode of administration (Table I and Ref. 25).

The renal clearance of plasma-unbound digoxin after oral administration of ^{3}H-β-methyldigoxin was 159 ± 8 ml/min ($n = 2$) and was significantly less than that after intravenous administration, 222 ± 32 ml/min ($n = 5$).

The renal clearance of the water-soluble metabolite fraction taken as an entity can be estimated from the observed rates of renal elimination, $\Delta U/\Delta t$ (Fig. 3), obtained in these studies at the respective plasma levels,

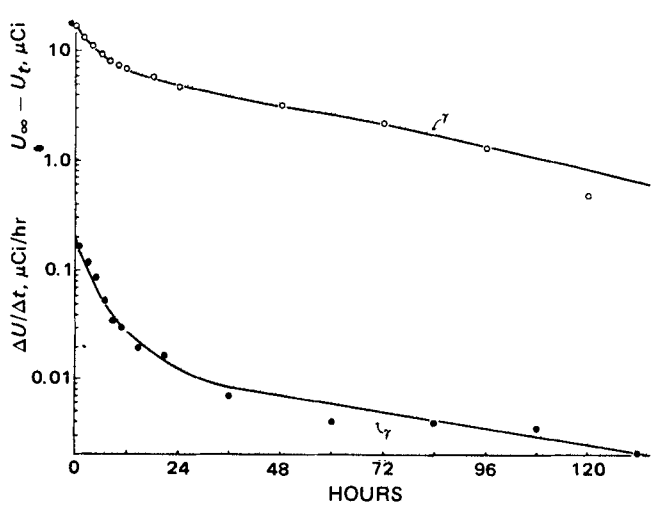


Figure 3—*Typical semilogarithmic plots of amounts of water-soluble metabolites yet to be excreted, $U_\infty - U_t$ (○), and rates of urinary excretion of water-soluble metabolites, ΔU/Δt (●), against time after oral administration: 120.1 μCi = 279 μg of β-methyldigoxin to Subject C with an apparent terminal half-life of 40 hr.*

Table II—Estimates of First-Pass Metabolism on Oral Administration

Parameter	Subject A (66.3 kg, 169 cm, 1.76 m² surface area)		Subject B (71.3 kg, 179 cm, 189 m² surface area)		Subject C (67.4 kg, 166 cm, 175 m² surface area)		Average ± *SD*
D, dose, μg	284	604	271	588	278	621	
$10^2\ U^{DIG}_{144\ hr}/D$							
Actual[a]	29.1	28.4	45.3	24.1	18.6	26.2	28.6 ± 9.0
Predicted[b]	22.4	17.4	22.9	17.9	18.5	14.1	18.9 ± 3.3
$10^2\ U^{H_2O}_{144\ hr}/D$							
Actual[c]	9.9	12.3	4.7	6.4	14.2	6.3	9.0 ± 3.8
Predicted[d]	3.6	3.4	2.1	3.1	1.7	5.2	3.2 ± 1.2
Percent of dose metabolized on first pass and excreted in urine:							
Digoxin[e], $10^2\ (U_{DIG}/D)_{first\ pass}$	6.7	11.0	22.4	6.2	0.1	12.1	9.8 ± 7.5
H_2O solubles[e], $10^2\ (U_{WS}/D)_{first\ pass}$	6.3	8.9	2.6	3.3	12.5	1.1	5.8 ± 4.3
Percent of dose metabolized to digoxin on first pass[f], $10^2(E_{DIG}/D)_{first\ pass}$	8.8	14.4	29.3	8.1	0.1	15.8	12.8 ± 9.8
Percent of dose metabolized to water solubles on first pass[g], $10^2\ (E_{WS}/D)_{first\ pass}$	10.5	14.4	—	4.7	25.0	—	9.1 ± 9.7
Total percent of dose metabolized on first pass[h], $[10^2\ (E_{DIG} + E_{WS})/D]_{first\ pass}$	19.3 (20.7)	28.8 (14.5)	29.3 (26.0)	12.8 (15.2)	25.1 (20.3)	15.8 (20.9)	21.9 ± 6.9 (19.6 ± 4.2)

[a] Calculated from the micrograms of β-methyldigoxin equivalent of the digoxin renally excreted at 144 hr, $U^{DIG}_{144\ hr}$, after oral administration of a dose of β-methyldigoxin, *D*, in micrograms. [b] Calculated from the product of the absorption efficiency of β-methyldigoxin (determined from the ratio of β-methyldigoxin renally excreted 144 hr after oral and intravenous administration) and the percent of the dose renally excreted as digoxin 144 hr after intravenous administration (Table I). [c] Calculated from the micrograms of β-methyldigoxin equivalent of the water-soluble metabolites renally excreted at 144 hr, $U^{H_2O}_{144\ hr}$, after oral administration of a dose of β-methyldigoxin, *D*, in micrograms. [d] Calculated from the product of the absorption efficiency of β-methyldigoxin [based on $U^{BMD}_{144\ hr}$ (po)/$U^{BMD}_{144\ hr}$ (iv) values of Table I] and the percent of the dose renally excreted as water-soluble metabolites 144 hr after intravenous administration. [e] Difference between actual and predicted values. [f] Amount of digoxin as percent of the dose formed on first pass, $10^2\ (E_{DIG}/D)_{first\ pass}$, can be estimated from the percent dose metabolized on first pass that is excreted in the urine, $10^2\ (U_{DIG}/D)_{first\ pass}$, *i.e.*, $10^2\ (E_{DIG}/D)_{first\ pass} = 10^2\ (U_{DIG}/D)_{first\ pass} \times (Cl_{DIG})_{tot}/(Cl_{DIG})_{ren}$, where the values for $(Cl_{DIG})_{tot}$ = 290 ml/min and $(Cl_{DIG})_{ren}$ = 222 ml/min were taken from the values obtained in the intravenous studies. An alternative method of estimation, on the premise that only digoxin is significantly formed on first pass and that all water solubles are derived from systemic digoxin and excreted in urine, is from $10^2\ (E_{DIG}/D)'_{first\ pass} = 10^2\ (U_{WS}/D)_{first\ pass} \times (Cl_{DIG})_{tot}/(Cl_{DIG})_{met}$, where $(Cl_{DIG})_{tot}$ = 290 ml/min and $(Cl_{DIG})_{met}$ = 68 ml/min. These $10^2\ (E_{DIG}/D)'_{first\ pass}$ values averaged 25 ± 18 (*SD*), larger than the averaged estimate of $10^2\ (E_{DIG}/D)_{first\ pass}$ = 12.2 ± 9.8 (*SD*). Although the standard deviations were large, it was concluded that water-soluble metabolites probably were not formed on first pass. [g] The total amount of water-soluble metabolites as a percent of dose, $10^2\ (E_{WS}/D)_{first\ pass}$, may be calculated from $10^2\ (U_{WS}/D)_{first\ pass} \times (Cl_{WS})_{tot}/(Cl_{WS})_{ren} - 10^2(E_{DIG}/D)_{first\ pass} \times (Cl_{DIG})_{met}/(Cl_{DIG})_{tot}$, where the latter term containing a ratio of the digoxin clearances of 0.234 corrects for water-soluble metabolites produced that result from the additional digoxin available systemically on first pass. The ratio of the water-soluble clearances in the first term on the right (the term that estimates the total amount of water solubles produced from that renally excreted) is taken as 2, since the data of Abshagen *et al.* (43) demonstrated relatively equal amounts of water solubles eliminated in the bile and urine on β-methyldigoxin administration. [h] The parenthetical values give the analog computer estimates of the total first-pass metabolism calculated from the ratio $k_{GIGI'}/(k_{GIGI'} + k_{GIB})$ (Scheme I).

$[A_p]$, of water-soluble metabolites obtained from the data of Rietbrock and Abshagen (26), where both sets of data were obtained after oral administration. No significant plasma levels of water-soluble metabolites were obtained in our studies. The average rates of renal elimination in the three subjects were 1.03, 1.16, 0.56, 0.41, and 0.27% of the total dose of radioactivity excreted per hour during 0–2-, 2–4-, 4–6-, 6–8-, and 8–10-hr intervals, respectively. The average plasma concentrations of water-soluble metabolites were 0.061, 0.070, 0.039, 0.023, and 0.013% of the dose of radioactivity per liter of plasma at 1, 3, 5, 7, and 9 hr, respectively, in the studies of Rietbrock and Abshagen (26). The respective individual quotients for the renal clearance of water-soluble metabolites, $(Cl^{H_2O}_p)_r = dU/dt/[A_p]$, were 17.0, 16.6, 14.4, 17.8, and 20.8 liters/hr and averaged 288 ± 17 ml/min.

The ratio of the renal clearance of water-soluble metabolites to creatinine clearance was 2.1 ± 0.1, indicating an excess of tubular secretion in addition to glomerular filtration.

An apparent linear terminal γ-phase with an average half-life of 36 hr was obtained from the semilogarithmic plots of $\Delta U/\Delta t$ and $U_\infty - Ut$ *versus* time for the water-soluble metabolites (Fig. 3). The slopes of these plots were similar to those observed for the terminal elimination γ-phase of the parent drug (40 hr). This terminal phase of the water-soluble metabolite fraction probably is dependent on its formation rather than its elimination, and the rate-limiting step probably is the rate of return of the parent drug from its deepest compartment, T'', with the overall rate constant of elimination of the water-soluble metabolites being a much faster process.

Absorption Efficiency and Evidence for First-Pass Metabolism—When the plasma concentrations and cumulative urine content of ^{3}H-β-methyldigoxin and digoxin were plotted against time in terms of the percent of the β-methyldigoxin dose per liter of plasma and the percent of dose, respectively, for the two dose levels of ^{3}H-β-methyldigoxin, the curves were superimposable for intravenous (25) and oral (Fig. 2) administration. Thus, the pharmacokinetics of β-methyldigoxin are dose independent, and the Dost principle (27) of corresponding areas is applicable to determine the degree of absorption. The areas (Table I) under the plasma concentration–time curves were estimated by graphical integration.

For the β-methyldigoxin curves, the area after oral absorption was 59 ± 6% of the area after intravenous administration and agreed with the fact that 60 ± 4% of the amount of β-methyldigoxin renally excreted at 144 hr and at infinite time after intravenous administration was renally excreted after oral administration. For the concentration of total radioactivity in plasma against time curves, the area after oral absorption was 76 ± 2% (n = 13) of the area after intravenous administration and was independent of dose. The amount of total radioactivity renally excreted after oral administration in 144 hr was 83 ± 3% (n = 14) of the amount renally excreted after intravenous administration. The relative percent renally excreted, oral–intravenous, did not reach reasonable constancy until after 24 hr, the minimum time that can be used for preliminary estimations of bioavailability.

This discrepancy between apparent oral absorption efficiencies from β-methyldigoxin and total radioactivity data indicates that ^{3}H-β-methyldigoxin was metabolized prior to its arrival in the systemic circulation, a first-pass phenomenon (28). This result is confirmed by the fact that apparent absorption efficiencies calculated from urinary excretion data (Table I) for digoxin (0.92 ± 0.12) and water-soluble me-

Table III—Parameters for β-Methyldigoxin Pharmacokinetics on Oral Administration Obtained by Analog Computer Fitting to Scheme I

Parameter	Subject A (66.3 kg, 169 cm, 1.76 m² surface area)		Subject B (71.3 kg, 179 cm, 1.89 m² surface area)		Subject C (67.4 kg, 166 cm, 1.75 m² surface area)		Average ± SD
D, dose, μg	284	604	271	588	278	621	—
$10^4\ k_{BT}$, sec^{-1} [a]	23.3	23.2	23.4	23.4	20.2	30.5	23.3 ± 0.1
$10^4\ k_{TB}$ [a]	15.1	20.8	12.3	12.3	13.4	11.2	15.1 ± 4.0
$10^4\ k_{BT'}$ [a]	7.71	6.97	5.62	5.62	5.53	7.18	6.43 ± 0.96
$10^4\ k_{T'B}$ [a]	1.79	2.46	0.979	0.979	1.08	0.947	1.37 ± 0.62
$10^4\ k_{BT''}$ [a]	3.44	1.79	3.30	3.30	4.76	4.80	3.57 ± 1.12
$10^4\ k_{T''B}$ [a]	0.120	0.135	0.125	0.125	0.141	0.146	0.132 ± 0.010
$10^4\ k_{BU}$ [a]	0.865	0.599	1.16	0.880	0.979	0.979	0.910 ± 0.19
$10^4\ k_{BM}$ [a]	1.18	1.03	0.469	0.870	1.63	1.43	1.10 ± 0.41
$10^4\ k_{M_1T}$ [b]	13.5	13.5	7.72	7.75	15.1	13.8	11.9 ± 3.3
$10^4\ k_{TM_1}$ [b]	10.4	12.5	3.78	3.80	7.66	2.55	6.78 ± 4.05
$10^4\ k_{M_1T'}$ [b]	11.1	13.4	5.77	5.75	8.38	8.45	8.81 ± 3.01
$10^4\ k_{T'M_1}$ [b]	0.156	0.146	0.177	0.162	0.120	0.162	0.154 ± 0.019
$10^4\ k_{M_1U}$ [b]	2.65	2.46	1.37	2.53	1.45	2.10	2.09 ± 0.56
$10^4\ (k_{M_1M_2} + k_{M_1\ \text{bile}})$ [b]	0.438	1.12	0.474	1.29	2.09	1.44	1.14 ± 0.63
$10^4\ k_{GIB}$ [b]	9.16	6.41	10.4	5.76	1.33	5.73	6.46 ± 3.16
$10^4\ k_{GIGI}$ [b]	2.39	1.09	3.64	1.03	0.339	1.51	1.67 ± 1.18
$10^4\ k_{GI'M_1}$ [b]	0.276	0.859	0.714	0.766	0.938	0.766	0.720 ± 0.23
V_p [u], liters [c]	14.5	14.5	13.4	13.4	7.02	7.02	11.7 ± 3.6
$(V_p)_{DIG}$ [d]	15.2	15.8	28.0	10.5	14.9	16.0	16.7 ± 5.9
$(V_D)_{DIG}$ [e]	1121	1479	997	404	1088	935	1004 ± 350
Absorption lag time, min [f]	24	8	8	17	7	8	12.0 ± 7.0

[a] Values for the microscopic rate constants of distribution and elimination were slightly modified to obtain the best fit from those obtained from the best analog computer fits of the plasma and urine data after intravenous administration (25). [b] Obtained from the best analog computer fit of the oral data with consideration of a lag time and a first-pass effect. The k_{GIB} corresponds to the intrinsic rate constant of absorption of unchanged drug absorbed. Its value is not expected to be coincident with the k_a value in Table I. The value for the latter was obtained by feathering and corresponds to the sum of the intrinsic rate constant and parallel first-order rate constant for the loss of the drug from the GI tract by other processes than absorption of unchanged drug. The value for $k_{M_1M_2} + k_{M_1\ \text{bile}}$ is 112% of $k_{M_1M_2}$, since the biliary clearance of digoxin is 12% of its total clearance (25). [c] Average values for both intravenous doses for the apparent volumes of distribution of the central compartment referenced to unbound drug in plasma were obtained from the best analog computer fit of the intravenous plasma data according to a four-compartment body model. The values of the volume of distribution of the central compartment in the oral experiments were postulated to be the same as in the intravenous experiments. [d] Values for the apparent volume of distribution of the central compartment referenced to total (bound and unbound) digoxin in plasma were obtained from the best analog computer fit of the data according to a three-compartment body model. [e] The value of the overall steady-state volume of distribution of digoxin was calculated (44) from $(V_p)_{DIG}[1 + (k_{MT'}/k_{TM}) + (k_{MT'}/k_{T'M})]$. [f] Determined from the best analog computer fits of the oral plasma data under the presumption of a first-pass phenomenon.

tabolite (1.9 ± 0.8) renal excretion were greatly in excess of the absorption efficiency of β-methyldigoxin (0.60). The area under the less precise plasma digoxin level–time curves after oral absorption of ^{3}H-β-methyldigoxin was 84 ± 10% of that area after intravenous administration and was confirmatory. A more detailed analysis of this first-pass phenomenon is given in Table II and indicates that 21.9 ± 2.8% (or 19.6 ± 1.7% by analog computer fitting) of the orally administered dose was metabolized in the GI lumen, gut wall, and/or the liver prior to absorption: 12.8 ± 4.0% to digoxin and 9.1 ± 4.0% (n = 4) to water-soluble metabolites.

Both digoxin and water-soluble metabolites probably are formed during the first pass and reach the systemic circulation. The extent of this total 22% first-pass metabolism in light of an estimated metabolic efficiency for β-methyldigoxin of 8% (25) implies a significant prehepatic first-pass metabolism. The former value, taken with the 60% absorption of β-methyldigoxin as such, implies that 18% does not reach the systemic circulation. The difference between the fecal recoveries of radioactivity between oral and intravenous administration, 25.9 ± 3.3 − 11.8 ± 0.7 = 14.1% (Table I), provides an alternative and similar estimate of the amount of material that does not reach the systemic circulation as β-methyldigoxin, digoxin, or other metabolites after oral administration. This amount may be an overestimate if the first-pass phenomenon after oral administration produces metabolites that are preferentially biliary excreted.

Evidence for an acid-catalyzed degradation of β-methyldigoxin *in vitro* and *in vivo* was given by Beerman (29), who determined individual radioactivities aspirated from the GI contents of volunteers administered labeled drug in polyethylene glycol. Non-β-methyldigoxin products were 28 and 15% of the total radioactivity in the gastric and duodenal aspirates, respectively, 10–15 min after drug administration. Their parameters of β-methyldigoxin absorption were similar to those found in this study; lag times were ~10 min, and peak concentrations occurred at ~50 min. β-Methyldigoxin incubated at pH 1.0 for 1 hr degraded 70% to digoxin, digoxigenin, and mono- and bisdigoxigenin digitoxosides. However, these three latter potential metabolites did not comprise any significant portion of the dose (<1%). The implication that the extent of the first-pass phenomenon may be a consequence of GI retention time was not confirmed by any apparent correlation with lag time for the studies in Table II.

Total radioactivities were measured in plasma and urine for 24 hr after administration of ^{3}H-β-methyldigoxin tablets. Peak plasma concentrations of 0.78 ± 0.17% of the administered radioactivity per liter were observed at 94 ± 21 min after administration. The corresponding value for the solutions given orally were 0.89 ± 0.11 at 72 ± 13 min (n = 11) after administration. A lag period of 15.8 ± 2.0 min between administration and the start of absorption was observed with the tablets compared to a lag period of 6.7 ± 1.6 min (n = 11) with the oral solutions; the latter was of the magnitude of the 5-min gastric emptying time of fluids in fasting individuals (30).

The ratios of the areas under the plasma concentration–time curves and the urinary excreted amounts of total radioactivity in 24 hr, corrected for the dose, were used to estimate the bioavailability of the tablets with respect to the solutions. They were 0.56 ± 0.05 and 0.92 ± 0.06 in plasma and urine, respectively, for tablets relative to the intravenous solutions and 0.87 ± 0.03 and 1.02 ± 0.05 in plasma and urine, respectively, for tablets relative to oral solutions. These findings indicate relatively complete absorption of β-methyldigoxin from the tablets relative to the solutions.

Pharmacokinetic Models for Orally Administered Solutions of β-Methyldigoxin and Digoxin and Their Fitting by Analog Computer—The existence of a first-pass metabolism of β-methyldigoxin was indicated by the fact that a greater percentage of the dose was excreted after oral administration relative to intravenous administration as the metabolite digoxin, M_1, and as the water-soluble metabolites, M_2 (Table II). The four-compartment body model for β-methyldigoxin and the three-compartment body model for the metabolite digoxin, developed previously for the intravenous case (25), were modified by adding a GI compartment to which the drug was administered with first-order absorption of β-methyldigoxin to the central compartment with rate constant k_{GIB} and with first-order generation of digoxin, M_1, with rate constant k_{GIM_1} to the central compartment of digoxin, M_1. Attempted analog computer fitting of the orally administered plasma β-methyldigoxin data to this model, using the microscopic rate constants obtained by fitting the intravenous data, consistently predicted initial plasma concentrations and urinary excreted amounts of digoxin greater than those actually observed. When this model was modified to include a first-pass metabolism directly to water-soluble metabolites in their

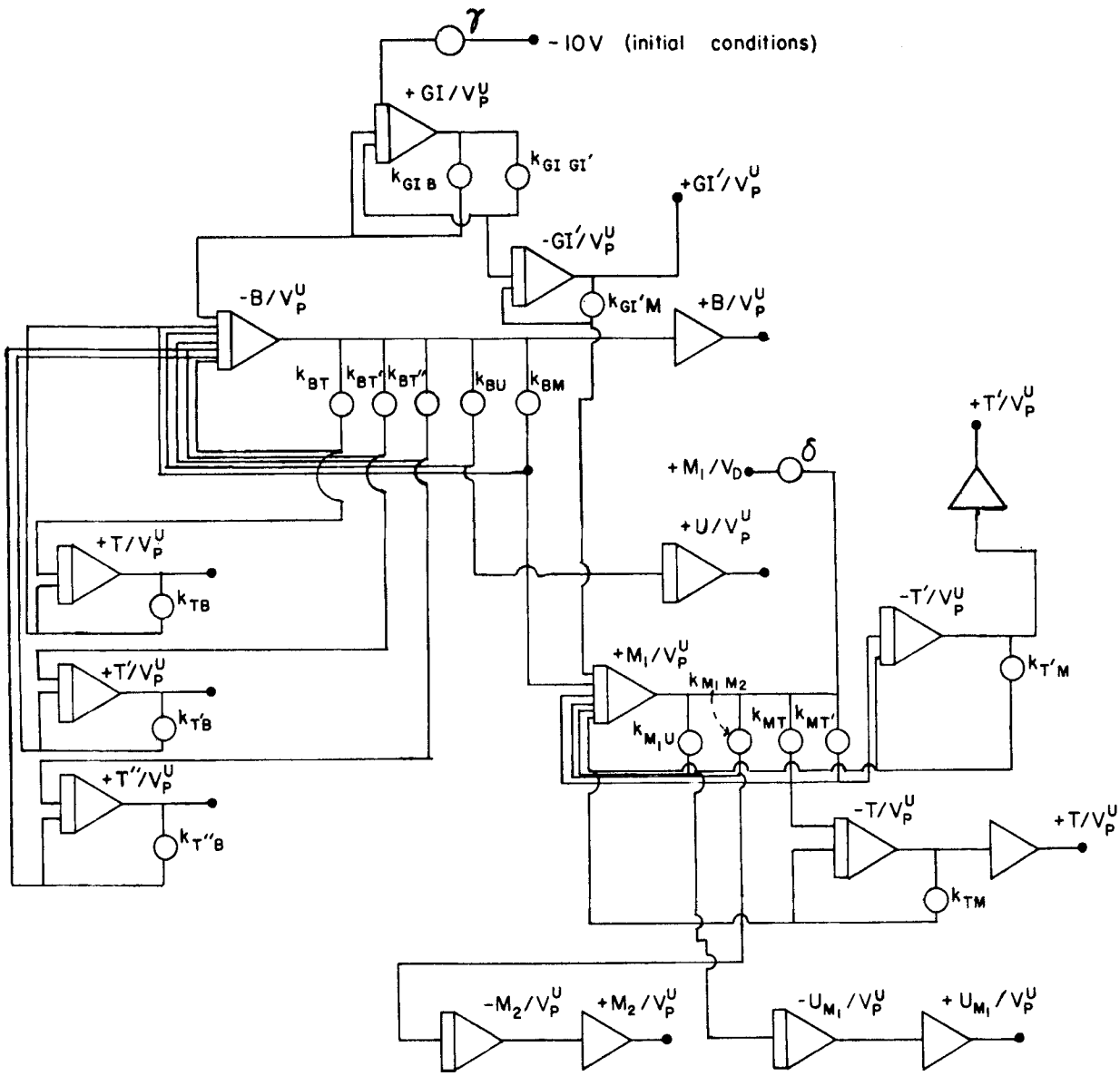
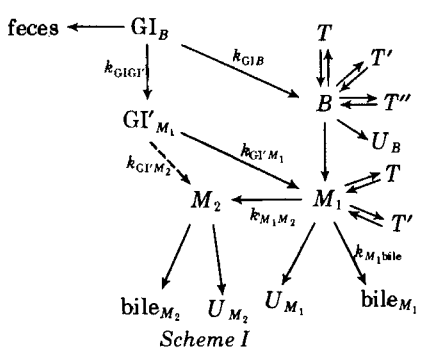


Figure 4—*Analog computer program to fit simultaneously the model of Scheme I to the experimental plasma and urine data where* $k_{GI'M_2}$ *is omitted and only* M_2 *as* $M_2/V_p{}^u$ *is generated. The route of* M_1 *to bile*$_{M_1}$ *is also omitted. Thus,* $k_{M_1M_2}$ *in the program and Table III was actually* $k_{M_1M_2} + k_{M_1 bile}$*, which overestimated the former by 12% since the biliary clearance of digoxin was estimated to be 36 ml/min out of a total clearance of 290 ml/min for digoxin in the intravenous studies* (25).

central compartment, the predicted cumulative terminal urinary amounts of digoxin generated by the analog computer were consistently lower than those actually observed.

These facts can be rationalized by postulating a delayed absorption of GI-generated digoxin, M_1, and/or water-soluble metabolites, M_2. Two alternative models are given in Scheme I, with and without the pathway indicated by the dashed line of rate constant $k_{GI'M_2}$. These models presume a significantly retarded production and absorption of GI-produced digoxin, $GI'M_1$, which is consistent with the literature reports (31) that digoxin is absorbed in the lower part of the small intestine and would be characterized by first-order rate constants $k_{GI,GI'}$ and $k_{GI'M_1}$, respectively. The plasma β-methyldigoxin and digoxin experimental values in concentration per liter were fitted to Scheme I (omitting the pathways characterized by $k_{GI'M_2}$ and k_{M_1bile}) by the analog computer program of Fig. 4. Concomitantly, the data for amounts of drug and metabolites in urine divided by the apparent volume of distribution of the central compartment for β-methyldigoxin, $(V_p{}^u)_{BMD}$, obtained in the intravenous studies were fitted.

Initial estimates of the amount of β-methyldigoxin absorbed either as drug or metabolites were made from the urinary recovery of unchanged drug and metabolites after multiplying by their respective ratios of total clearance to renal clearance. However, the initial condition, placed on



Scheme I

the GI_B compartment representing the dose, D, of ^{3}H-β-methyldigoxin that was actually absorbed as drug or metabolites [divided by this apparent volume of distribution $D/(V_p{}^u)_{BMD}$], was varied to give the best fit of the model since it cannot be presumed that the total dose, either as drug or metabolites, was transferred to the body. The $GI_B \rightarrow$ feces in Scheme I represents the route of fecal elimination of the total dose of ^{3}H-β-methyldigoxin not absorbed as drug or metabolite.

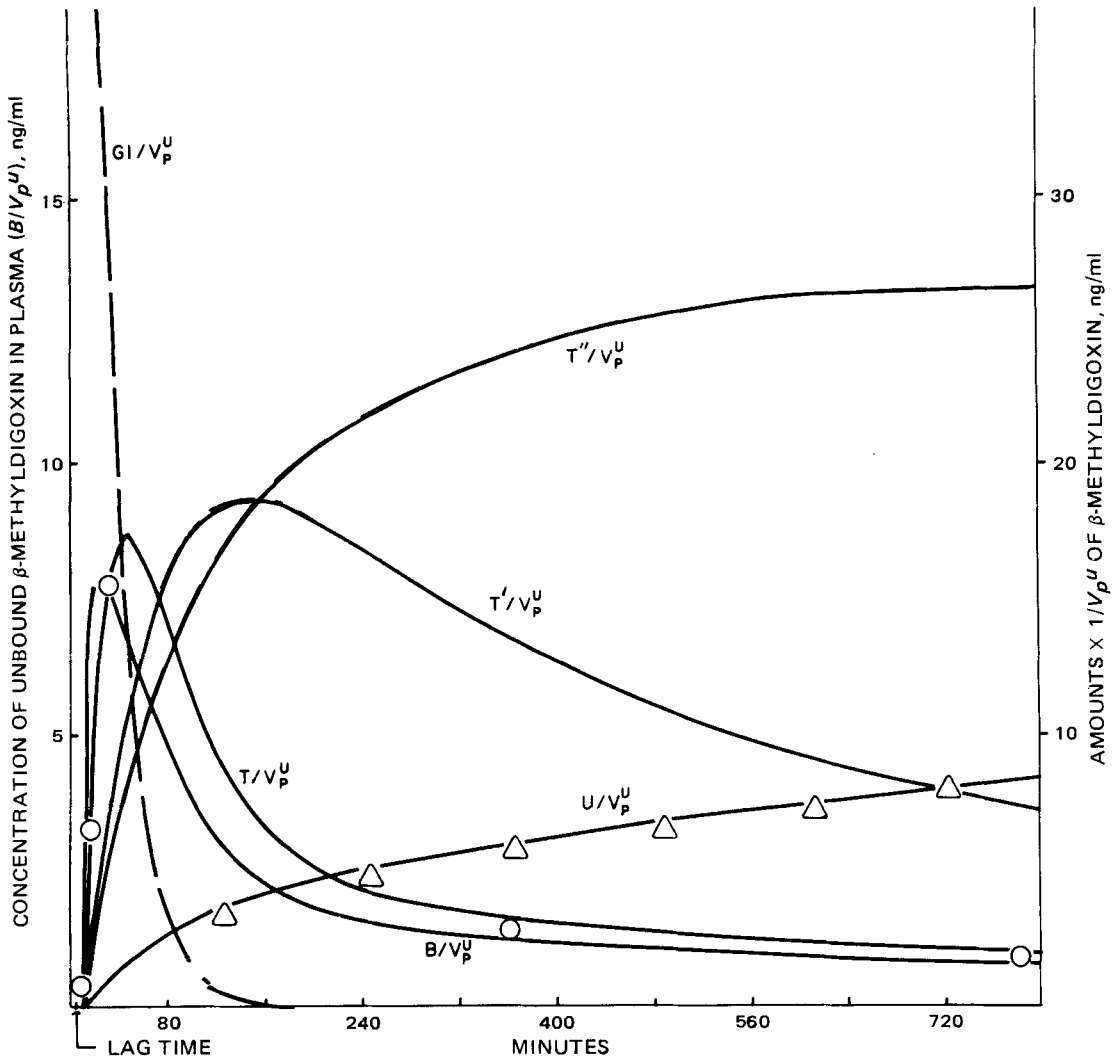


Figure 5—*Typical analog computer fitting of plasma water (unbound drug) concentration (O, left scale) and urine (Δ, right scale) data of β-methyldigoxin for 0.6-mg oral solution administration to Subject C over 13 hr in accordance with a four-compartment body model and a first-pass effect. All data are given as per milliliter of the volume of distribution of the central compartment referenced to unbound β-methyldigoxin, and the apparent concentrations of drug in the various tissues (GI, T, T′, and T″) and urine (U) (right scale) are generated with the parameters of Table III.*

The simultaneous analog computer fitting of the plasma and urine generated drug and metabolite amounts in peripheral tissues, urine, and the GI tract in terms of arbitrary concentrations (*i.e.*, amounts divided by $V_p{}^u$). The generated plasma concentrations of the metabolite $M_1/(V_p{}^u)_{BMD}$ were multiplied by a constant $\delta = (V_p{}^u)_{BMD}/(V_p)_{DIG}$ to fit best the plotted metabolite $M_1/(V_p)_{DIG}$ data so that the apparent volume of distribution, $(V_p)_{DIG}$, of M_1 could be calculated from the obtained values of δ. Lag times of absorption, 8–24 min, had to be assumed to fit best the first portion of the β-methyldigoxin data. Good fits always were obtained for the drug concentration in plasma and urine and the apparent concentration of M_1 in urine—*viz.*, $U_{BMD}/(V_p{}^u)_{BMD}$ and $U_{M_1}/(V_p{}^u)_{BMD}$; typical examples are given in Figs. 5 and 6. Only minor adjustments in the values of the microscopic rate constants found in the intravenous experiments were necessary to give optimal fits of the oral data. Their values are given in Table III.

Comparisons of Bioavailabilities of Orally Administered β-Methyldigoxin and Orally Administered Digoxin—The intrinsic bioavailability of unchanged ^{3}H-β-methyldigoxin after oral administration of solutions with respect to intravenous administration was 59.5 ± 3.3% (n = 12), evaluated by both renal excretion and areas under the unbound plasma level–time curves (Table I). The values ranged from 41 to 74% among all subjects, although urinary excretion estimates ranged only from 50 to 67% and, if one value was discarded, from 57 to 67%. However, this finding does not completely characterize the pharmacodynamic availability of such oral solutions since cardioactive digoxin is formed systemically (25, 32) from β-methyldigoxin and from first-pass prehepatic and hepatic metabolism of orally administered β-methyldigoxin (Table II). It was estimated previously (25) that the fraction of digoxin formed from the systemic β-methyldigoxin was 40% of the intravenously administered dose (34.5% renally eliminated and 5.5% biliary excreted). Thus, 0.40 × 60 = 24% is the amount of the total oral dose of ^{3}H-β-methyldigoxin absorbed as such that delivers digoxin to the body. The cardioactive digoxin formed by the first pass that reaches the systemic circulation as such (Table II) was 12.8 ± 4.0%. A total of 60 + 13 = 73% of digoxin plus β-methyldigoxin is absorbed.

However, the total systemic bioavailability of these cardioactive agents, digoxin plus β-methyldigoxin, on the premise of pharmacodynamic equivalence and similar terminal overall elimination rates of ~40 hr half-life, would be 60% (as β-methyldigoxin delivered directly) +24% (as digoxin derived from systemic β-methyldigoxin) + 13% (as digoxin derived from first-pass transformation of β-methyldigoxin prior to absorption) = 97%. On the same premise of pharmacodynamic equivalency of β-methyldigoxin and digoxin, intravenous β-methyldigoxin would deliver 100% (as β-methyldigoxin) + 40% (as digoxin derived from systemic β-methyldigoxin) = 140% of an equivalent dose of intravenously administered digoxin. Thus, the oral pharmacodynamic bioavailability of β-methyldigoxin relative to its intravenous administration would be 97/140 = 69%, where the oral pharmacodynamic bioavailability of β-methyldigoxin relative to equimolar intravenously administered digoxin, on the premise of equimolar pharmacodynamic equivalency, is 97%. These calculations were based on the presumption that the metabolites other than digoxin did not possess cardioactivity.

The proper comparison of the relative bioavailabilities of orally administered β-methyldigoxin and orally administered digoxin should be

Table IV—Critical Evaluations of Solution and Solid Dosage Form Oral Bioavailabilities of Digoxin Referenced to Intravenous Administration from Major Studies in the Literature

Reference	Oral Vehicle	Assay	Mean Estimated Absorption Efficiency, %	Method of Evaluation	Comments	Dose, mg	t_{max} (approx), min	$C_{max,po}$, % Dose/Liter of Plasma
33[a]	Ethanol, 95%	Total radioactivity	85[b]	Fecal excretion represents unabsorbed material, 7 days	Fecal excretion method criticized in Refs. 31 and 36 and herein; intravenous and oral population differed, > 20 subjects; total excretion in urine and stools; 49% oral and 85% intravenous	1.0, 2.0	70	—
			46[b]	Oral–intravenous, relative urinary excretion[c], 7 days				
31	Polyethylene glycol solution	Radioactivity of separated digoxin	50[b]	Intestinal aspirates	Based on oral studies only, five subjects	0.25	60	—
35	5% Dextrose solution	Radioimmunoassay	80[b]	Oral–intravenous, relative area under curve, 0–96 hr	Two subjects	0.50	30	0.75
37	40% Propylene glycol–10% ethanol	Radioimmunoassay	100, 93[b,c]	Oral–intravenous, relative urinary excretion, 10 days	Only 57% of intravenous dose recovered in urine of four subjects, well below other reported values	0.50	90	0.70
39	40% Propylene glycol–10% ethanol	Radioimmunoassay	81, 87[c,d] (50–115% range for 0.125 mg) 68, 61[c,d] (53–89% range for 0.25 mg)	Oral–intravenous, relative area under 0–24 hr curve for daily chronic dose	Gross inconsistencies of bioavailability estimates within the five or six subjects from different methods; apparent dose dependency by area and steady-state serum digoxin methods	0.125, 0.25 daily	60	—
			94, 96[c,d] (69–116% range for 0.125 mg) 82, 88[c,d] (71–122% range for 0.25 mg)	Oral–intravenous, relative mean steady-state serum levels				
			83, 87[c,d] (48–126% range)	Oral–intravenous, relative urinary excretion in 24 hrs				
36	5% Propylene glycol–10% ethanol	Radioimmunoassay	78[b]	Oral–intravenous, area under curve, 0–80 hr	—	1.0	75	0.70
			75[b] (57–96% range)	Oral–intravenous, relative urinary excretion, 12 days				
35	Tablet[e]	Radioimmunoassay	57	Oral–intravenous, relative area under curve, 0–96 hr	Two subjects, 70% bioavailability relative to oral solution	0.50	—	0.30 (0.15 and 0.44)
37	Tablet[e]	Radioimmunoassay	70[b] (49–80% range)	Oral–intravenous, relative urinary excretion, 10 days	Only 57% of intravenous dose recovered in urine of four subjects, well below other reported values, 78% bioavailability relative to oral solution	0.50	100	0.38
			62[b] (48–80% range)	Oral–intravenous, relative area under curve				

39	Tablet[e]	Radioimmunoassay	58, 61[c,d] (50–80% range) 64, 87[c,d] (49–111% range)	Oral–intravenous, relative area under 0–24-hr curve; 100% bioavailability[c] relative to oral solution Oral–intravenous, relative urinary excretion in 24 hr; 100%[c] bioavailability relative to oral solution	Gross inconsistencies of bioavailability estimates within the five or six subjects from different methods	0.25 daily	60	—
			65, 69[c,d]	Oral–intravenous, relative mean steady-state serum levels; 78% bioavailability relative to oral solution				
36	Tablet[e]	Radioimmunoassay	64[b] 63[b] (44–82% range)	Oral–intravenous, area under curve, 0–80 hr Oral–intravenous, relative urinary excretion, 12 days	82% bioavailability relative to oral solution 84% bioavailability relative to oral solution	1.0–1.5	75	0.36
40	Capsule	Total radioactivity	79.8 ± 3.7[b]	Oral–intravenous, relative area under 0–∞-hr curves		0.25	75	0.84
			80.2 ± 8.8[b]	Oral–intravenous, relative urinary excretion				
41	Not cited	Total radioactivity	69.7 ± 7.0	Oral–intravenous, relative urinary excretion, 0–96 hr			75	

[a] And references therein. [b] Acute administration. [c] Evaluated from data given in reference. [d] Daily chronic administration; data evaluated at last 2–3 days of 14-day dosing. [e] Presumably standard Lanoxin tablets.

based on crossover studies of specifically quantified separated drug and metabolites monitored in the same subjects where the results from intravenous administration of both drugs are used as relative standards. An alternative is to compare such independent studies on each drug. Surprisingly, no bioavailability comparisons of digoxin oral solutions and intravenous administrations have been attempted with specific assays of drug and metabolites in the same subjects. In general, estimates of absorption efficiency of digoxin in the literature were made by nonspecific methods using total radioactivity or radioimmunoassay.

Beerman *et al.* (31) were especially critical of a claim (33) for 85% oral absorption from a solution with different subject populations. The claim was based on the assumption that the fecal excretion of radioactivity within 5 days represented unabsorbed material since the total recovery in urine and feces averaged only 49% within 7 days. They suggested that polar metabolites may have been lost on chloroform extraction of fecal radioactivity and that digoxin decomposition before absorption was not considered. The criticism (31) of this paper (33) appears justified. The renally excreted percent of administered tritiated digoxin in Table 2 of Ref. 33 showed that the apparent bioavailability of an orally administered solution to that intravenously administered for more than 20 subjects was 100 × 34% (po)/74% (iv) = 46%, a far cry from the 85% estimated.

The urinary excretion of intravenously administered tritiated digoxin in six other patients, with biliary fistula and bile from the T-tube completely collected, was 58.5% of the dose, indicative of a minimum of 100 × {[74% (iv) − 59% (iv, fistula)]/74% (iv)} = 20% enterohepatic recirculation of digoxin. The presumption would be the same made by Doherty *et al.* (33) that the two populations, with and without bile collection, were similar. A direct measurement of biliary excretion was 8.1 ± 1.4% (*SEM*), which was significantly less then the 20% estimated. However, since 1.3 ± 0.4% (*SEM*) fecal excretion was observed with the biliary collection, it was obvious that the T-tube was not completely effective and that the 7–8% estimate (33) of enterohepatic recycling was an underestimate. The fecal excretion of non-biliary-cannulated subjects on intravenous administration was reported as 11.3 (33) and 14.8% (34). Beerman *et al.* (31) demonstrated significant decomposition of orally administered digoxin in the GI tract and claimed that absorption of intact digoxin administered in water solution was approximately 50%.

Wagner *et al.* (35) were critical of their own estimate of 80% oral bioavailability as digoxin of a 5% dextrose solution relative to intravenous bioavailability as performed in two subjects, 78.3 and 82.0%, respectively. Areas under the radioimmunoassay plasma level–time curves were used for evaluation; it was admitted that any gastroenterohepatically formed metabolites, as by first pass, would have led to overestimation. It was also stated that the use of total radioactivity and radioimmunoassay methods make extensive pharmacokinetic analysis tenuous.

Johnson *et al.* (36), who also used radioimmunoassay, studied intravenous and oral solution absorption of digoxin in eight volunteers. They estimated that oral absorption from an elixir was 78% of the intravenous absorption by the area under the curve method and 75% by urinary excretion, with the latter ranging from 57 to 96% in different subjects. This was admittedly not digoxin *per se*. The absorption of digoxin from tablets[3] relative to intravenous administration varied between 44 and 82% in different subjects with a mean of 64%. These authors were also critical of the previously mentioned claim of 85% relative absorption (33) and a similar claim of high relative absorption (37) of a 40% propylene glycol solution. In the latter case, the stated percentage urinary excretion of injected digoxin by radioimmunoassay was well below other reported values; other investigators could only claim 65% relative absorption for such an elixir (38).

When steady-state procedures were used to estimate the relative bioavailability by the authors that had previously claimed high absorption (37), the absolute bioavailability of a digoxin solution relative to intravenous bioavailability was only radioimmunologically estimated as either 77 or 87%, depending on the magnitude of the oral dose (39). However, when the bioavailability estimates within an individual by the different methods used are compared, gross inconsistencies become apparent and cast suspicion on the averaged estimates. All of these radioimmunoassay studies can be criticized for their nonspecificity. In addition, Huffman *et al.* (39), who studied apparent dose dependency, claimed that the area under the curve after oral digoxin solution administration was not proportional to dose. If true, this finding signifies that such a method for estimating relative bioavailability is not valid for digoxin.

Estimates of oral absorption efficiencies, relative to intravenous administration in the same subjects, with presumably optimumly bioa-

[3] Lanoxin.

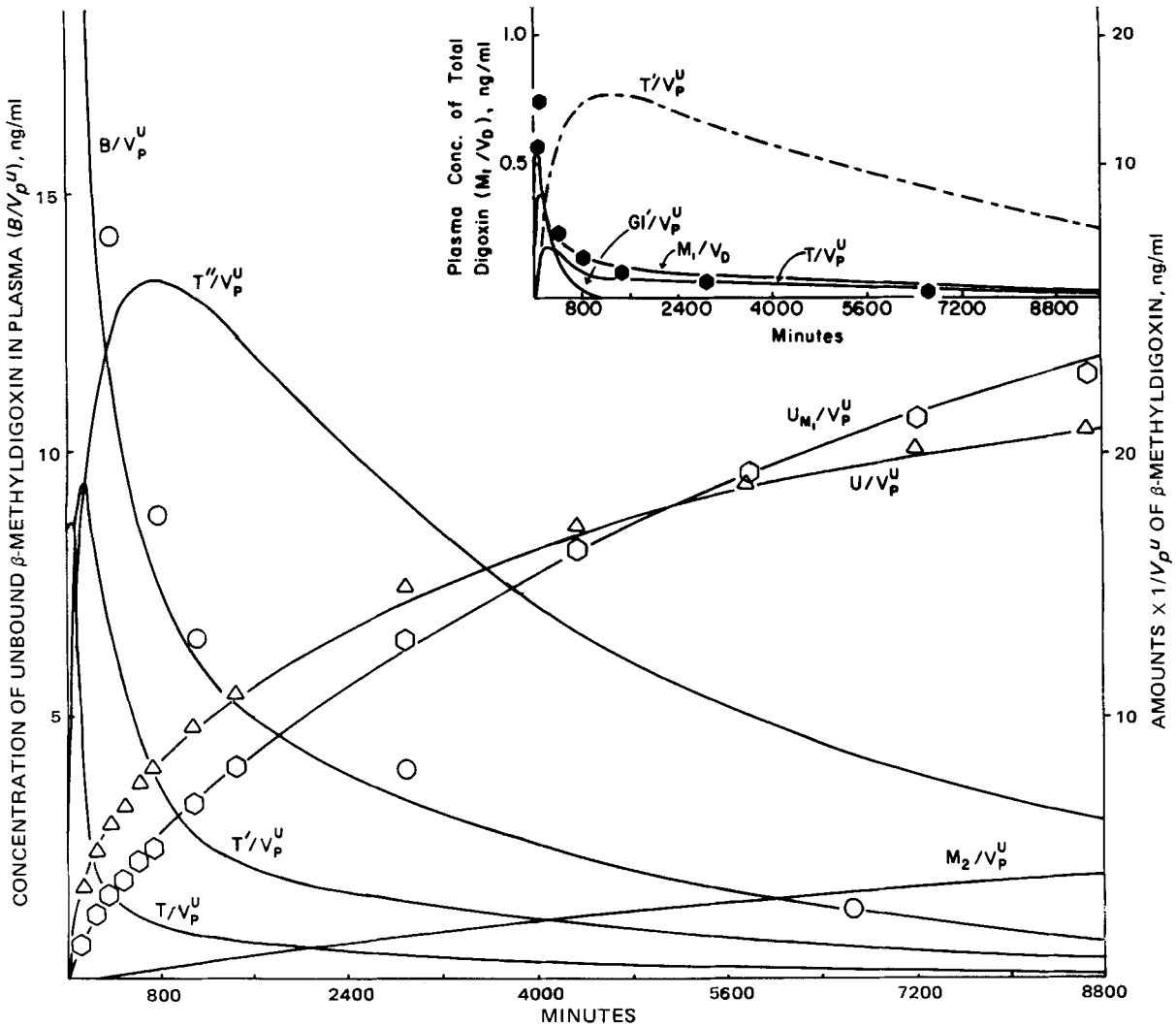


Figure 6—*Typical analog computer fitting of plasma water (unbound drug) concentration (○, left scale) and urine (△) data of β-methyldigoxin and (○) digoxin (right scale) for 0.6-mg oral solution administration to Subject C over the full time scale of 144 hr. All data are given as per milliliter of the volume of distribution of the central compartment referenced to unbound β-methyldigoxin, except for the plasma digoxin data (●) in the inset which are given as the observed concentration in terms of its own volume of distribution, V_D. The apparent concentrations of β-methyldigoxin in its various tissues (T, T′, and T″) and GI tract (GI′), M_2 in the body, and digoxin in its tissues (T and T′) are generated (right scale) with the parameters of Table III.*

vailable tablets where radioimmunoassay was used, included 57% by area methods (35) and 62% (39) and 64% (36) by urinary excretion. In one instance of total radioactivity measurements, the estimate for oral absorption efficiency of solid dosage forms compared to intravenous administration was 80.2 ± 8.8% for digoxin (40). In another, based on 96-hr urine collections, the estimates were 69.7 ± 7% for digoxin and 90.7 ± 13.1% for β-methyldigoxin (41). However, the fact that no digoxin was found in these urines (41) as a β-methyldigoxin metabolite is confusing in light of our consistent recovery of approximately equivalent amounts of ^{3}H-digoxin and ^{3}H-β-methyldigoxin in urine after ^{3}H-β-methyldigoxin administration (Table I).

A critical summary of the best estimates of absolute bioavailability of oral digoxin solution and solid dosage forms relative to intravenous administration is given in Table IV.

The appearance of a peak plasma concentration for orally administered digoxin solutions of 0.70–0.75% of total dose/liter of plasma by total assay methods at about 60–90 min (Table IV) is not inconsistent with the oral solution absorption data of β-methyldigoxin based on total radioactivity with a peak plasma level of 0.89 ± 0.11% at 72 ± 13 min and a lag time of 6.7 ± 1.6 min (n = 11). The tablet data for β-methyldigoxin showed comparable values of 0.78 ± 0.17% at 94 ± 21 min with a lag time of 15.8 ± 2.0 min but were significantly greater than the 0.37% values shown in several cases for administered digoxin tablets (36, 37).

In summary, oral absorption of digoxin from solutions and tablets varies widely with the individual (Table IV), consistent with the arguments that GI or other prehepatic degradations are the determining processes in digoxin bioavailability. Specific analytical procedures have not been generally attempted for digoxin. Thus, mean bioavailability estimates of oral solutions of digoxin assayed by methods nonspecific for digoxin relative to intravenous administration range from 50 to 93% (Table IV). Comparatively, the radioactivity absorbed for β-methyldigoxin solutions was 76 ± 2% by the area method and 83 ± 3% by urinary excretion at 144 hr compared to intravenous administration. β-Methyldigoxin plus its derived metabolite digoxin had a systemic bioavailability of 59.5 ± 3.3% as β-methyldigoxin and 12.8 ± 4.0% as digoxin for a total of 72% relative to intravenous administration in these studies using specific analysis.

It is difficult to state conclusively that β-methyldigoxin was more effectively and reproducibly absorbed than digoxin administered *per se* on oral administration based on this evidence because of the obvious difficulty in appraising the digoxin studies in the literature. Such a decision can only be made if proper crossover intravenous and oral solution studies of β-methyldigoxin and digoxin are made in the same subjects using specific analyses of the separated drug and metabolites.

However, there are suggestions of advantages of β-methyldigoxin relative to digoxin. β-Methyldigoxin apparently delivers more cardioactive agent per mole administered than digoxin. In these studies, there was more consistency in measured oral bioavailability among and within individuals (Table I) than had been indicated for digoxin (36, 39). If this finding indicates that β-methyldigoxin has a more reproducible

availability within and among individuals, it is clinically significant. The tablet studied had a bioavailability equivalent to that of the oral solution by the criteria used. Although a pilot-plant production lot rather than a normal production lot was used, the study indicates that a tablet of β-methyldigoxin can be made that is equivalent to an oral solution, something that cannot be said for digoxin.

There are several possible rationales as to why β-methyldigoxin may have properties that could favor it over digoxin. The observed 11-fold greater water solubility[4] of β-methyldigoxin (46 mg/100 ml at pH 7.5 and 22°) over digoxin (4 mg/100 ml) implies the relatively greater rate of dissolution of β-methyldigoxin. On the premise that the dissolution rate from solid dosage forms is the limiting step in glycoside availability from tablets, this property should favor β-methyldigoxin. The fact that β-methyldigoxin, notwithstanding its greater aqueous solubility, is a less polar compound than digoxin (42) and has a higher partition coefficient into chloroform—*viz.*, 85.1 to digoxin's 9.4 (41), implies that its penetration of the lipid-like GI wall may be more facile than digoxin and thus abet a more reproducible and possibly more complete absorption (3).

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