Pharmacokinetics of β-Methyldigoxin in Healthy Humans III: Pharmacodynamic Correlations

PETER H. HINDERLING * and EDWARD R. GARRETT ˣ

Abstract □ Significant decreases in left ventricular ejection time and heart rate were observed after the oral and intravenous administration of β-methyldigoxin. The time course of this action correlated with the time course of β-methyldigoxin and its active metabolite, digoxin, in their deepest pharmacokinetic compartments and not with their plasma levels. This pharmacodynamic activity peaked (decrease of 6.3% at 0.6 mg iv and 3.5% at 0.3 mg iv; decrease of 3.8% at 0.6 mg po and 4.5% at 0.3 mg po) at about 10 hr, concomitantly with the amounts of β-methyldigoxin in its deepest compartment and showed a terminal half-life equivalent to the 41 hr for β-methyldigoxin. The relative peak heights and area under the ejection time–time curves indicated a linear dose–response relationship on intravenous administration and an effect greater than that reported for larger amounts of digoxin. The time course of heart rate action correlated (8.3 and 12.5% decreases with 0.3 and 0.6 mg iv, respectively; 6.5 and 9.5% decreases with 0.3 and 0.6 mg po, respectively) with the time course of β-methyldigoxin and its metabolite digoxin in shallower pharmacokinetic compartments (peaks at ~80 min intravenously and 135 min orally), and significant effects had disappeared by 10 hr after drug administration. This finding indicated that the biophases differ for ejection time and heart rate action. Mean arterial blood pressure could not be correlated with the time course of drug, although a small consistent decrease (4–8%) was observed from 22 to 72 hr after drug administration.

Keyphrases □ β-Methyldigoxin—oral and intravenous, effect on left ventricular ejection time and heart rate correlated with pharmacokinetic parameters, humans □ Pharmacokinetics—β-methyldigoxin, oral and intravenous, correlated with effect on left ventricular ejection time and heart rate, humans □ Pharmacodynamics—β-methyldigoxin, oral and intravenous, effect on left ventricular ejection time and heart rate correlated with pharmacokinetic parameters, humans □ Cardiac glycosides—β-methyldigoxin, oral and intravenous, effect on left ventricular ejection time and heart rate correlated with pharmacokinetic parameters, humans

Cardiac glycosides have been shown to exert positive inotropic and negative chronotropic effects both in patients with congestive heart failure (1, 2) and in healthy subjects (3–5). Effects on the left ventricular performance are reflected in shortening of the left ventricular ejection time interval (LVET) when corrected for the heart rate. Noninvasive methods can monitor glycoside effects on these cardiovascular parameters (6).

Few attempts have been made to correlate simultaneously measured pharmacokinetics and pharmacodynamics of glycosides (7, 8). In many cases, both the parent drug and some of its metabolites are pharmacologically active (9). The availability of a specific assay is mandatory to correlate specifically the observed effects and the individual kinetics of the parent drug and its active metabolites. Such correlations may lead to the proper characterization of the biophases of drug and metabolite action.

β-Methyldigoxin undergoes significant metabolism to active metabolites such as digoxin in humans (10, 11) and has demonstrated positive inotropic and negative chronotropic effects in patients with congestive heart failure and in healthy subjects (12, 13). The purposes of these studies were to monitor such pharmacodynamic parameters with time in normal volunteers administered 0.3 and 0.6 mg of β-methyldigoxin both orally and intravenously and to relate these effects with the previously evaluated pharmacokinetics of the drug and its metabolites (11, 14).

EXPERIMENTAL[1]

The left ventricular ejection time derived from the external carotid pulse[2] and the heart rates[3] were simultaneously recorded on a three-channel recorder[4] (paper speed of 50 mm/min). The left ventricular ejection time was measured from the beginning of the upstroke to the trough of the incisura (2). The heart rate was calculated from the quotient 60/(average RR interval) of at least 10 consecutive beats (3). Besides the standard ECG, a vector ECG was recorded on a three-channel recorder[5]. The blood pressure was measured according to Korotkov, using an inflatable cuff connected to a mercury manometer on the left a brachialis. The diastolic blood pressure was measured during phase 5.

For all measurements, each individual was in a prostrate position. The subjects were prostrate during the first 24 hr after β-methyldigoxin administration and then were ambulant. They were in a prostrate position for at least 30 min prior to and during measurements taken between 24 and 144 hr after drug administration. Details of the concomitant pharmacokinetic studies on β-methyldigoxin were given previously (11, 14).

Sufficient control values were taken in each study prior to drug administration before and after the placement of the needle and the catheter. The carotid arterial pulse and the ECG's were taken continuously up to 30 min, at 5-min intervals up to 60 min, at 15-min intervals up to 4 hr, at 30-min intervals up to 11 hr, and then at 12-hr intervals up to 72 hr after drug administration. In some experiments, the measurements were expanded to 132 hr.

The left ventricular ejection time values were determined in Subjects A–F. Subject G was excluded because the beginning of the upstroke could not be defined clearly in his carotid pulse recordings. The experimentally determined values were normalized (3) for the heart rate, HR:

$$\text{LVETI} = \text{LVET} + 0.0016 \times \text{HR} \qquad \text{(Eq. 1)}$$

where LVETI is the left ventricular ejection time index. The stroke volume, SV, was calculated (2) for the control period from:

$$\text{SV} = \frac{\text{LVETI} - 0.266 + (0.0017 \times 82)}{0.0017} \qquad \text{(Eq. 2)}$$

and the cardiac output, CO, for the control period was calculated from:

$$\text{CO} = \text{SV} \times \text{HR} \qquad \text{(Eq. 3)}$$

The LVETI values were expressed as percent of the control values taken prior to drug administration (Table I).

The blood pressure was measured in Subjects A–G at 5-min intervals up to 30 min, at 15-min intervals up to 4 hr, at 30-min intervals up to 11 hr, and then at 12-hr intervals up to 72 hr after drug administration. The mean arterial blood pressure was calculated by adding to the diastolic pressure one-third of the difference between the experimental systolic and diastolic pressures (15). The cardiac outputs measured during the control period before drug administration ranged between 5390 and 6257 ml/min in all four studies and all individuals and were normal (16).

[1] The volunteers were informed orally and in writing of any and all potential risks and of the experimental protocol prior to the studies; verbal consent and written consent were obtained. The human experimentation, radioactive substance, and clinical research committees of the Health Center, University of Florida, reviewed and approved the research protocol prior to the studies. A physician was in attendance during the studies.

[2] Pulse wave pickup, Hewlett-Packard Co., Palo Alto, Calif.

[3] Standard-ECG, Lead II, Hewlett-Packard Co., Palo Alto, Calif.

[4] Hewlett-Packard Co., Palo Alto, Calif.

[5] Marquetter patient transmitter, Marquette Electronics, Milwaukee, Wis.

Table I—Control Values of LVETI, RR Interval, and Heart Rate prior to Drug Administration

LVETI, sec	Subject	Number of Measurements	RR Interval (±*SD*), sec	Average Heart Rate
0.410 ± 0.0062	D	8	1.122 ± 0.368	53
0.392 ± 0.0063	E	8	0.962 ± 0.098	62
0.389 ± 0.0061	F	8	1.083 ± 0.108	55
0.395 ± 0.0059	G	8	1.111 ± 0.106	54
0.408 ± 0.0032	A	8	1.062 ± 0.060	57
0.403 ± 0.0090	B	8	1.134 ± 0.075	53
0.400 ± 0.010		48	1.079 ± 0.099	56

RESULTS AND DISCUSSION

Tolerance of β-Methyldigoxin—No systematic changes were found in the clinical laboratory data obtained in the subjects prior to each of the four administrations of β-methyldigoxin (11, 14). In particular, the serum sodium and potassium concentrations, reportedly critical (16) for the myocardial glycoside uptake and effect, were within the normal range for all subjects and all studies. The administered β-methyldigoxin was well tolerated at the two dosage levels (0.6 and 0.3 mg) and by both the oral and intravenous routes. No adverse cardiac effects were observed.

Pharmacodynamic Action on Left Ventricular Ejection Time of β-Methyldigoxin and Digoxin on β-Methyldigoxin Administration—The LVETI and RR values obtained for each volunteer during the control period prior to oral and intravenous administration of drug at two dosage levels are listed in Table I. The LVETI values for all subjects were within the normal range of 0.395 ± 0.017 for healthy male adults (6). Plots of the percent LVETI decrease against time, averaged for all subjects, showed a maximal decrease at 10–22 hr after both dosages of β-methyldigoxin administered intravenously or orally (Figs. 1 and 2).

The subsequently decreasing effect on the LVETI was observable for the 132-hr (0.6 mg iv) and 72-hr periods of observation (0.3 mg iv, 0.6 and 0.3 mg po), respectively.

Reuning *et al.* (8) stated that the percent LVETI decrease observed with time by Shapiro *et al.* (7) can be best correlated with tissue levels of digoxin generated by the analog computer from plasma levels on the basis of a two-compartment body model for digoxin. The pharmacokinetics of both β-methyldigoxin and the active main metabolite, digoxin, have to be considered to correlate the magnitude and time course of the LVETI effect on β-methyldigoxin administration.

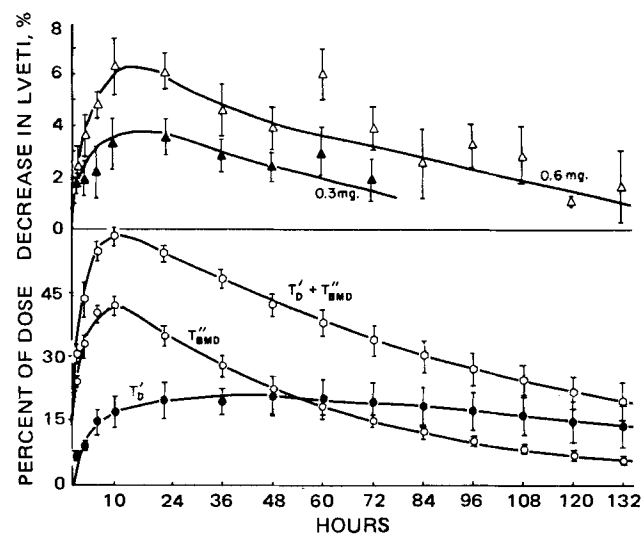


Figure 1—*Apparent correlation between the mean percent LVETI decrease at 0.3 (▲) and 0.6 (△) mg of β-methyldigoxin (BMD) and the mean amounts of β-methyldigoxin (○) and digoxin (●) in their respective deepest tissues, T_{BMD}'' and T_D', and in their sum (○) in percent of the administered intravenous dose of β-methyldigoxin as a function of time. The LVETI values obtained prior to drug administration served as controls. The vertical bars indicate ±1 SEM of the means. The amounts in the tissues were generated by the analog computer from the best fits of the experimental plasma and urine data for all studies. They are given as percent of dose and are valid for both dose levels since the intravenous pharmacokinetics were independent of dose (11).*

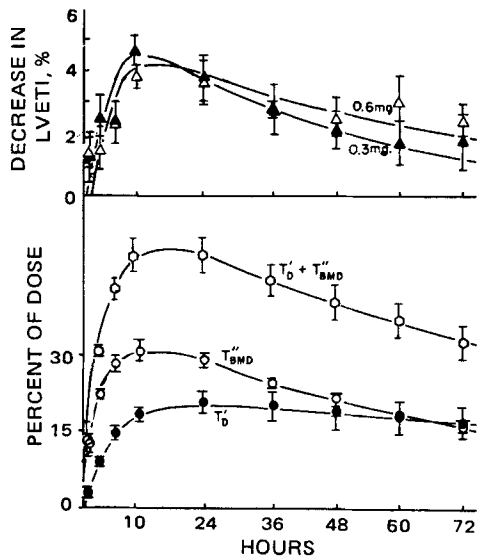
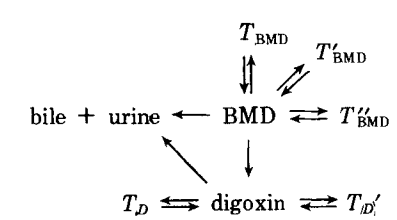


Figure 2—*Apparent correlation between the mean percent LVETI decrease at 0.3 (▲) and 0.6 (△) mg of β-methyldigoxin and the mean amounts of β-methyldigoxin (○) and digoxin (●) in their respective deepest tissues, T_{BMD}'' and T_D', and in their sum (○) in percent of the administered oral dose of β-methyldigoxin as a function of time. The LVETI values obtained prior to drug administration served as controls. The vertical bars indicate ±1 SEM of the means. The amounts in the tissues were generated by the analog computer from the best fits of the experimental plasma and urine data for all studies. They are given as percent of dose and are valid for both dose levels since the oral pharmacokinetics were independent of dose (14).*

Statistically significant negative linear correlations existed between the averaged LVETI effect and both the averaged amounts of parent drug in its deepest compartment, T_{BMD}'', and the averaged amounts of digoxin in its deepest compartment, T_D', for both modes of administration and both dose levels (Table II, Scheme I, and Figs. 1 and 2). The amounts of β-methyldigoxin and digoxin in these tissues as percent of the dose were generated by the analog computer from the best fit of the experimental data in plasma and urine (11, 14). No such correlations could exist between the LVETI effect and the amounts of drug in the other tissues or plasma since the maxima of the former (Figs. 1 and 2) occurred well after the maximum values of the latter (11, 14). The peak amounts of the sum of β-methyldigoxin in the moderately deep tissues, T_{BMD}' and T_D, occurred at 80 and 135 min for intravenous (Figs. 3 and 4) and oral (Fig. 5) administration, respectively. The peak amounts in the plasma and shallower tissues such as T_{BMD} occurred much earlier (Fig. 5) (11, 14). The assumption of a linear relationship between drug content in the deepest tissues and its effect on ventricular performance during the time course of both cannot be excluded.

The peak effect of the averaged LVETI decrease occurred at 10–22 hr after drug administration for both dosage levels and routes (Figs. 1 and 2). The β-methyldigoxin amounts in T_{BMD}'' peaked at 10–12 hr after intravenous administration and at 13 hr after oral administration. The



Scheme I—Simplified pharmacokinetic model for the distribution of β-methyldigoxin from its central compartment to its successively deeper tissues in the order T_{BMD}, T_{BMD}' and T_{BMD}'' and for the distribution of metabolically generated digoxin to its successively deeper tissues in the order T_D and T_D'.

Table II—Correlations[a] between Amounts[b] of β-Methyldigoxin and Digoxin in Their Respective Tissue Compartments and the LVETI and Heart Rate Change

Dose, mg	Modes of Administration	LVETI *versus* T''_{BMD}	LVETI *versus* T_D'	Heart Rate *versus* T'_{BMD}	Heart Rate *versus* T_D
0.6	Intravenous	$r = -0.86, p \leq 0.01$	$r = -0.41, p \leq 0.20$	$r = -0.84, p \leq 0.01$	$r = -0.85, p \leq 0.01$
0.3	Intravenous	$r = -0.41, p \leq 0.50$	$r = -0.76, p \leq 0.02$	$r = -0.83, p \leq 0.01$	$r = -0.82, p \leq 0.01$
0.6	Oral	$r = -0.72. p \leq 0.05$	$r = -0.85, p \leq 0.01$	$r = -0.63, p \leq 0.10$	$r = -0.40, p \leq 0.10$
0.3	Oral	$r = -0.87, p \leq 0.01$	$r = -0.51, p \leq 0.20$	$r = -0.63, p \leq 0.01$	$r = -0.47, p \leq 0.05$

[a] r is the correlation coefficient, and p is the probability of estimate that the correlation is random. [b] As percent of β-methyldigoxin dose.

amounts of digoxin in T_D' were at maximum considerably later, at 34 or 43 hr after intravenous administration and at 20–29 hr after oral administration (11, 14).

Maximum decreases of the LVETI of 5.6 and 7.2% were reported in healthy volunteers by 6 hr after 1.6 and 1.0 mg iv of digoxin, respectively (5, 7). After 3.2 mg po of digoxin, a maximum decrease of 4.7% was reported at 12–24 hr after dosing (5). These values are not inconsistent with what was observed herein for β-methyldigoxin: maximum decreases of LVETI of 6.3 and 3.5% at about 10 hr after 0.6 and 0.3 mg iv of β-methyldigoxin, respectively. It may even imply a greater potency for the β-methyldigoxin over digoxin at equivalent doses, consistent with the fact that intravenously administered β-methyldigoxin delivers 140% more cardioactive material than an equivalent dose of digoxin (14).

A linear dose–LVETI effect relationship was indicated for deslanoside (5). In the intravenous studies reported here, the maxima (6.3% for 0.6 mg and 3.5% for 0.3 mg of β-methyldigoxin) and areas under the effect–time curves up to 72 hr (364% hr for 0.6 mg and 197% hr for 0.3 mg of β-methyldigoxin) were proportional to the dose. This finding is indicative of a linear dose–effect relationship. In the oral studies, the observed maxima (3.8% for 0.6 mg and 4.5% for 0.3 mg) and areas under the effect–time curve up to 72 hr (205% hr for 0.6 mg and 192% hr for 0.3 mg of β-methyldigoxin) were practically the same for both dose levels. However, the variability in the effect data was larger in the oral studies.

Calculations of the bioavailability of the two oral dosages of β-methyldigoxin relative to the respective intravenous dose from the areas under the LVETI effect–time curves, with admittedly high variability, gave values of 60 and 100% for 0.6 and 0.3 mg, respectively. It was shown previously (14) for both doses that an orally administered β-methyldigoxin solution delivered 70% of the cardioactivity of an equivalent intravenous dose on the presumption that the drug and its metabolite, digoxin, had equivalent cardioactivity in the body.

Pharmacodynamic Action on Heart Rate of β-Methyldigoxin and Digoxin on β-Methyldigoxin Administration—Plots of the percent heart rate decrease against time, averaged for all subjects, showed significant decreases after drug administration with apparent maximal decreases of 8.3% at 150 min and 12.2% at 80 min for 0.3- and 0.6-mg iv doses, respectively, indicative of a dose dependency (Fig. 3). The amounts of β-methyldigoxin in compartment T'_{BMD} and of digoxin in T_D both peaked at approximately 80 min after intravenous administration of β-methyldigoxin (Figs. 3 and 4). After oral administration of β-methyldigoxin, maximal amounts were reached at about 135 min for β-methyldigoxin in T'_{BMD} and at 155 min for digoxin in T_D (Fig. 5), where maximal heart rate decreases were 6.5 and 9.5% at 90–120 and 90 min for 0.3- and 0.6-mg po doses, respectively. The variabilities in the data were too great to conclude dose dependence on oral administration.

Statistically significant linear negative correlations existed between percent heart rate effect and amounts in percent of the dose of β-methyldigoxin in its moderately deep compartment, T'_{BMD}, and of digoxin in its shallower compartment, T_D, for both modes of administration and both dose levels of β-methyldigoxin (Table II and Figs. 3–5) but not with the amounts in the deep compartments, T''_{BMD} and T_D' (Fig. 4).

The possibility that the observed decrease in heart rate is a procedural effect cannot be rigorously excluded since no placebo experiments were performed. However, similar significant decreases in heart rate in healthy volunteers were attributed to such glycosides (5).

Maximum heart rate decreases of 16% at 20–120 min and of 15% at 240

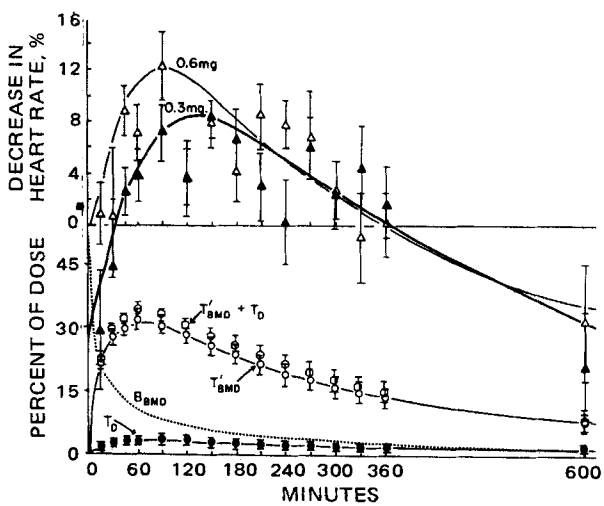


Figure 3—*Apparent correlation between the mean percent heart rate decrease at 0.3 (▲) and 0.6 (△) mg of β-methyldigoxin and the mean amounts of β-methyldigoxin (○) and digoxin (●) in their respective moderately deep tissues, T'_{BMD} and T_D, and in their sum (○) in percent of the administered intravenous dose of β-methyldigoxin as a function of time. The heart rate values obtained prior to drug administration served as controls. The vertical bars indicate ±1 SEM of the means. The amounts in the tissues were generated by the analog computer from the best fits of the experimental plasma and urine data for all studies. They are given as percent of dose and are valid for both dose levels since the intravenous pharmacokinetics were independent of dose (11). The dashed line shows the mean of the analog computer-fitted amounts of β-methyldigoxin in the central compartment, B_{BMD}, in percent of β-methyldigoxin administered as a function of time for comparison.*

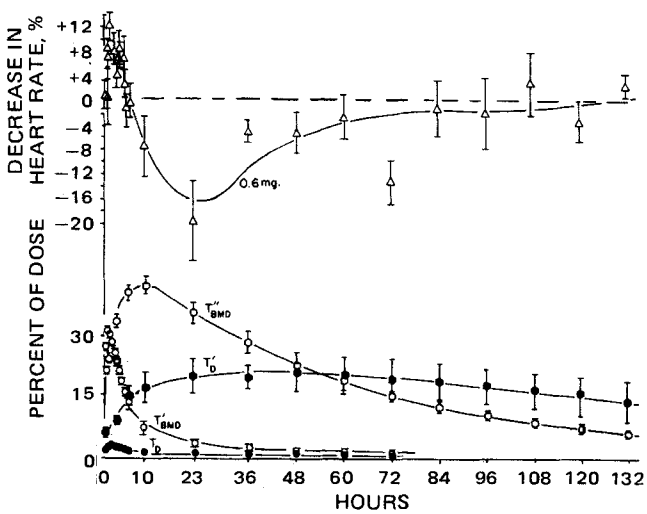


Figure 4—*Apparent correlation between the mean percent heart rate decreases at 0.6 mg (△) of β-methyldigoxin over 132 hr and the mean amounts of β-methyldigoxin (○) and digoxin (●) in their respective moderately deep tissues, T'_{BMD} and T_D, and in their sum (○) in percent of the administered intravenous dose of β-methyldigoxin as a function of time. The heart rate values obtained prior to drug administration served as controls. The vertical bars indicate ±1 SEM of the means. The amounts in the tissues were generated by the analog computer from the best fits of the experimental plasma and urine data for all studies and are given as the percent of the dose. The time course of the mean amounts of β-methyldigoxin (○) and digoxin (●) in their respective deepest compartments, T''_{BMD} and T_D', are shown for comparison in terms of the percent of administered dose. The increase in heart rate at 22 hr and subsequently is attributed to the fact that the previously prostrate patients became ambulatory at that time.*

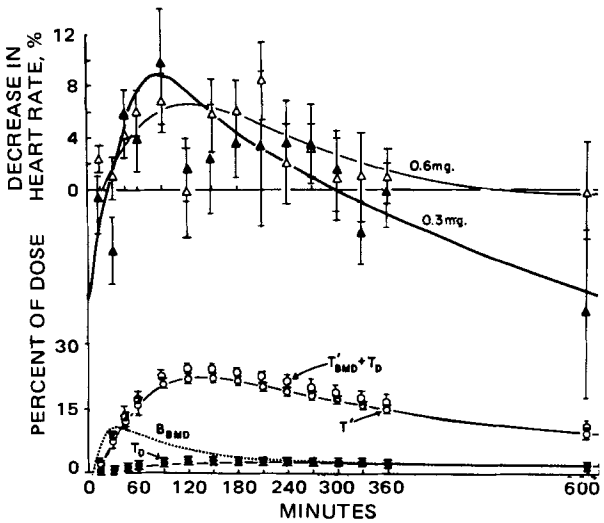


Figure 5—*Apparent correlation between the mean percent heart rate decreases at 0.3 (▲) and 0.6 (△) mg of β-methyldigoxin and the mean amounts of β-methyldigoxin (○) and digoxin (●) in their respective moderately deep tissues, T'_{BMD} and T_D, and in their sum (○) in percent of the administered oral dose of β-methyldigoxin as a function of time. The heart rate values obtained prior to drug administration served as controls. The vertical bars indicate ±1 SEM of the means. The amounts in the tissues were generated by the analog computer from the best fits of the experimental plasma and urine data for all studies. They are given as percent of dose and are valid for both dose levels since the oral pharmacokinetics were independent of dose (14). The dashed line shows the mean of the analog computer-fitted amounts of β-methyldigoxin in the central compartment, B_{BMD}, in percent of β-methyldigoxin administered as a function of time for comparison.*

min were reported after 1.6 mg iv and 3.25 mg po of digoxin, respectively (17, 18); intravenous injection of a placebo led to a maximal 3.3% heart rate decrease in these subjects. Maximal decreases in heart rate at 60–150 min were also observed in patients with coronary heart disease that were given 0.6 mg iv of β-methyldigoxin (19), consistent with our results.

Possible Differences in Apparent Biophases—The time course of this apparent negative chronotropic effect observed from heart rate measurements was remarkably different from the time course of the positive inotropic effect observed from LVETI measurements after β-methyldigoxin administration. Therefore, these two receptor site-containing biophases are kinetically different.

The mean arterial blood pressure was averaged for all subjects and showed a small, but consistent, decrease of 4–8%, 22–72 hr after administration for both doses and both modes of administration and was probably a procedural effect. The mean arterial blood pressure showed no consistent pattern, and the changes were small (±4%) during the first 22 hr.

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* Present address: Biozentrum, Der Universität Basel, 4056 Basel, Switzerland.

ˣ To whom inquiries should be directed.