Absolute Bioavailability and Dose Proportionality of Betaxolol in Normal Healthy Subjects

T. M. LUDDEN*x, D. A. BOYLE*, D. GIESEKER‡, G. T. KENNEDY§, M. H. CRAWFORD§, L. K. LUDDEN¶, AND W. A. CLEMENTI‡

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Abstract □ The absolute bioavailability and dose proportionality of betaxolol [(±)-1-(*p*-[2-cyclopropylmethoxy)ethyl]phenoxy]-3-(isopropylamino)-2-propanol hydrochloride], a cardioselective beta-adrenergic antagonist effective in the treatment of angina and hypertension, was studied in 12 healthy male subjects using a four-way crossover Latin Square design. Each subject received a 10-mg iv dose administered by constant-rate infusion over a period of 30 min and three oral doses (10, 20, and 40 mg). Blood and urine were collected over a 48-h period and analyzed for betaxolol using gas–liquid chromatography with electron capture detection. Maximum concentrations occurred 3–4 h after the dose. The maximum mean (±SD) blood concentrations normalized to the 10-mg oral dose were 21.6 ± 3.7, 21.1 ± 3.7, and 22.5 ± 4.0 μg/L following the 10-, 20-, and 40-mg doses, respectively. A significant lag time of 10–80 min was observed after oral doses but was not related to dose size. The terminal slope (t_s), absolute bioavailability (F), and renal clearance (CL_r) were likewise not affected to an important degree by dose (t_s: 0.043 ± 0.006, 0.044 ± 0.005, 0.046 ± 0.006 h^{-1}; F: 0.88 ± 0.08, 0.82 ± 0.06, 0.84 ± 0.07; CL_r: 0.68 ± 0.22, 0.69 ± 0.19, 0.65 ± 0.22 mL/min kg). Unlike many beta-adrenergic antagonists, betaxolol has a long half-life (13–20 h) and high and consistent bioavailability (70–90%), and its disposition is independent of the size of the administered dose.

Betaxolol hydrochloride [(±)-1-[*p*-[2-(cyclopropylmethoxy)ethyl]phenoxy]-3-(isopropylamino-2)-propanol hydrochloride] is a cardioselective beta-adrenergic antagonist.[1] Despite its lipophilicity (octanolol–water partition, log P = 0.59), initial pharmacokinetic studies suggested that a high fraction of orally administered betaxolol reaches the systemic circulation.[2–5] Other lipophilic beta-adrenergic antagonists, such as propranolol and metoprolol, are usually characterized by low bioavailability secondary to a moderate to high first-pass extraction.[6] In this respect, betaxolol appears to differ from other lipophilic beta-adrenergic antagonists. Betaxolol is a racemic mixture, but the kinetics of the enantiomers are not markedly different.[7]

Betaxolol has been shown to be effective in the treatment of angina[8] and hypertension[9–11] over the dose range of 10 to 40 mg administered once daily. Although the pharmacokinetics and disposition of betaxolol have been studied,[3–5, 12–14] there has not been a thorough investigation of betaxolol pharmacokinetics and renal excretion over the range of clinically used oral doses. Such information is necessary for the design of rational adjustments in betaxolol regimens during antihypertensive or antianginal therapy. Therefore, a four-period dose proportionality and absolute bioavailability study using clinically effective doses was performed to determine if the pharmacokinetics of betaxolol were independent of dose.

Experimental Section

Subjects and Study Design—Healthy, nonobese, nonsmoking adult male subjects were enrolled in the study after providing written, informed consent. The protocol and consent form were approved by the University of Texas Health Science Center San Antonio Institutional Review Board.

Each subject was randomly assigned into a four-way crossover, mutually orthogonal Latin Square design. On separate occasions, each subject received 10 mg of betaxolol HCl, diluted in 40 mL of sterile normal saline and administered by constant-rate iv infusion over a period of 30 min, and oral capsules containing 10, 20, or 40 mg of betaxolol HCl. Study subjects and the investigators were blinded with regard to the size of the oral doses. Subjects fasted for 8 h prior to drug administration and 4 h after drug administration. Oral doses were administered with 100 mL of water. Subjects remained recumbent for the first 3 h except for periodic measurement of standing heart rate and blood pressure. Supine heart rate and blood pressure were also obtained at selected intervals throughout the study.

One subject experienced postural hypotension associated with all oral doses and syncope after the 40-mg oral dose. This patient was not administered the iv dose and was excluded from the analysis. A thirteenth subject was enrolled to replace this individual. A total of 12 subjects (24.8 ± 2.6 years; 73.6 ± 7.5 kg) completed the study.

Sampling Procedure—For the iv doses, blood samples were obtained just prior to the beginning of the infusion, at 15 min into the infusion, at the end of the infusion, and then at 5, 10, 20, 30, and 45 min and 1, 1.5, 2, 3, 4, 6, 12, 24, 36, and 48 h after the end of the infusion. For the oral doses, the blood sampling was similar except that samples at 5 min after the dose were not obtained and there were no samples corresponding to those collected during the infusion. Urine was collected over the following intervals: 0–3, 3–6, 6–12, 12–24, and 24–48 h.

Analytical Method—The following analytical procedure was adapted from a previously published method[15] for the measurement of betaxolol in biological fluids. One milliliter of whole blood was mixed with 1.4 mL of deionized water, 10 μL of internal standard solution (*dl*-propranolol HCl, 2.3 ng/μL in methanol), and 0.1 mL of 2M NaOH in a screw-capped culture tube. The mixture was placed on a liquid–liquid extraction column (Chem Elute, Analytichem International, Harbor City, CA) and the culture tube was rinsed with 7 mL of freshly distilled ether. After 5 min the rinse was added to the extraction column. Two additional 7-mL and a final 5-mL aliquot of ether were added to the column at 5-min intervals. The total eluate was evaporated to ~200 μL under nitrogen at 40–50 °C. This concentrate was diluted to 6 mL with ether and the ether phase was extracted with 2.5 mL of 0.2 M HCl by mixing for 10 min on a mechanical shaker. After separation of phases by centrifugation, the ether phase was discarded and the acidic, aqueous layer was washed with an additional 5 mL of ether. The aqueous layer was then treated with 0.3 mL of 2 M NaOH and extracted with 5 mL of ether. The ether phase was transferred to a clean 16 × 125-mm screw-capped culture tube and evaporated to total dryness under dry nitrogen at 50 °C. To each tube was added 0.2 mL of a 1:9 (v/v) mixture of heptafluorobutyric anhydride (Sigma Chemical Company, St. Louis,

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MO) in ethyl acetate (Burdick and Jackson, Muskegon, MI). The tube was capped and heated at 50–60 °C for 15 min. Solvent and excess derivatizing reagent were then removed by evaporation under a stream of nitrogen at 50 °C. Each sample was reconstituted with 0.2 mL of ethyl acetate or hexane (Burdick and Jackson) and 3 μL was injected onto the chromatography column.

Chromatography was performed using a gas chromatograph equipped with a ^{63}Ni-electron capture detector (model 5710 Hewlett-Packard, Avondale, PA) and a glass column (5 ft × 2 mm i.d.) packed with 3% OV-7 100/120 Supelcoport (Supelco, Inc.). Chromatographic conditions were as follows: injection port, 250 °C; column, 195 °C; and detector, 350 °C. Carrier gas was 5% methane in argon at a flow rate of 34 mL/min. Peak heights were measured on a strip chart recorder (Hewlett-Packard model 7130A). The ratio of the peak height of the betaxolol peak to the internal standard peak was calculated, and standard curves (2–200 ng/mL) were calculated by linear least squares regression of the peak height ratios for standards against the known concentrations. The ratios were weighted by the reciprocal of the respective known concentrations expressed as betaxolol free base. The base concentration for each unknown sample was calculated from the slope and intercept of the regression equation. Each sample was assayed in duplicate. If the two results differed by >10% from the mean, a third assay was performed. If one of the three results was then disparate, it was deleted; otherwise, all three results were averaged. This assay has a coefficient of variation of 7–11% for single determinations.

The urine samples for an individual subject collected over a single study period were pooled in proportion to each original voided volume so as to provide a single sample for each study period for each subject. A 0.5-mL aliquot of each pooled urine sample was mixed with 2.4 mL of deionized water, 0.1 mL of 2 M NaOH, and 10 μL of internal standard (*dl*-propranolol HCl, 23 ng/μL). This mixture was extracted with 6 mL of freshly distilled ether. The remainder of the procedure was identical to that for whole blood with the following exceptions. First, the standard curves were prepared for the range 0.2–2 μg/mL. Next, a megabore crosslinked 50% phenyl, 50% methyl silicone column (10 m × 0.53 mm), with a 2.0-μm film thickness (HP-17, Hewlett-Packard, Avondale, PA), was used in the gas chromatograph (model 5890 Hewlett-Packard, Avondale, PA). The chromatographic conditions were as follows: injection port temperature, 250 °C; column temperature, 200 °C; detector temperature, 300 °C; carrier gas (5% methane in argon), 9.5 mL/min; split vent, 51 mL/min; makeup gas (methane:argon), 52 mL/min. The coefficient of variation (CV) for this procedure was 4–10% for a single determination, and each pooled sample was assayed in duplicate. Finally, peak heights were measured using a 3393A (Hewlett-Packard) integrator.

Pharmacokinetic Data Analysis—The highest observed concentration was designated C_{max}; and the time of this concentration relative to the time of dosing was designated t_{max}d. The t_{max}d was corrected for the apparent lag time (lag) and is t_{max}l (i.e., t_{max}l = t_{max}d − lag). The lag time was estimated graphically by back extrapolation of the initial rising phase of the concentration–time curve to zero concentration. An estimate of the absorption rate constant (K_a) for each individual was obtained by simultaneously fitting an open two-compartment kinetic model to the iv and oral data using the digital computer program NONMEM.[16] Preliminary nonlinear regression analysis of the data obtained after oral doses indicated that failure to include a lag time resulted in systematic bias. This bias could be eliminated by inclusion of a lag time estimated as described above. Therefore, the times for the oral data were corrected for the lag time estimated from each specific data set. Data for the iv doses were also analyzed alone to yield estimate of elimination clearance, distribution clearance, central volume of distribution, and steady-state volume of distribution. Residual intrasubject error was assumed to be proportional to the predicted concentration since the CV of the assay did not vary markedly with concentration. The terminal slope (*ts*) of each concentration–time profile was obtained by fitting a monoexponential equation to the terminal log–linear data points, again using NONMEM and a proportional error model. The total area under the concentration–time curve (AUC_∞) was obtained by linear trapezoidal approximation with correction to time infinity by dividing the last observed data point by the *ts* value. Renal clearance (CL_r) was calculated from the ratio of the amount of unchanged betaxolol excreted in urine over a period of 48 h (Xu_{48}) to the corresponding area under the curve (AUC_{48}). The ratio of AUC_{48} relative to AUC_∞ was used to calculate Xu_∞ from Xu_{48} as follows:

$$Xu_\infty = Xu_{48}(AUC_\infty/AUC_{48}) \quad (1)$$

The extent of bioavailability (F) was calculated using a correction for dose size and for the measured CL_r for each dose. Nonrenal clearance was assumed to be constant for all doses and was estimated as:

$$CL_{nr,iv} = CL_{total,iv} - CL_{r,iv} \quad (2)$$

Thus, the formula used to estimate F for each oral dose was:

$$F = \frac{AUC_{\infty,oral}Dose_{iv}(CL_{nr,iv} + CL_{r,oral})}{AUC_{\infty,iv}Dose_{oral}(CL_{nr,iv} + CL_{r,iv})} \quad (3)$$

Since all betaxolol concentrations were expressed as the free base, all doses of betaxolol HCl were corrected to reflect the content of the dose in terms of betaxolol free base (89.4%).

Statistical Analysis—General least squares analysis of variance was performed on each parameter using the SYSTAT (Systat, Inc., Evanston, IL) statistical package on an IBM-PCXT. If a significant difference was detected, then a Student-Newman-Keuls post-hoc test was performed to determine specific differences. An alpha level of 0.05 was used for all hypothesis tests. Asymmetric 95% confidence intervals were calculated for the ratios of the parameter values for the 20- and 40-mg oral doses relative to the parameter values for the 10-mg oral dose.

Results

The blood betaxolol concentration–time profiles for a typical subject are displayed in Figure 1. The profile following the iv infusion is indicative of a multicompartmental system. A two-compartment open model with zero-order input and first-order elimination adequately described the observed data for the individual iv doses for 10 subjects. A one-compartment model was sufficient for the remaining two subjects. The majority of profiles following the oral doses did not display a prominent multicompartmental character. Many of the profiles after oral doses yielded modest secondary peak concentrations. The excellent agreement in terminal slope (*ts*) among the doses, as shown in Figure 1, is representative of all subjects. All oral doses evidenced a short lag time prior to the beginning of absorption. The mean concentration–time profiles are shown in Figure 2.

The compartmental model parameters obtained for the iv doses were: elimination clearance, 3.44 ± 0.42 (SD) mL/kg min; intercompartmental clearance, 92.3 ± 59.2 mL/kg min, central volume of distribution, 0.781 ± 0.543 L/kg; and steady-state volume of distribution, 4.76 ± 0.78 L/kg. The

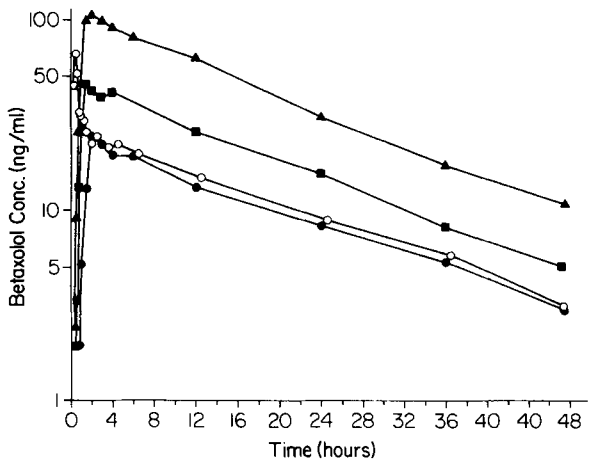

Figure 1—*Typical betaxolol concentration–time curves following a 10-mg iv dose administered by constant-rate infusion over a period of 30 min* (○) *and oral capsules containing 10* (●), *20* (■), *and 40 mg* (▲).

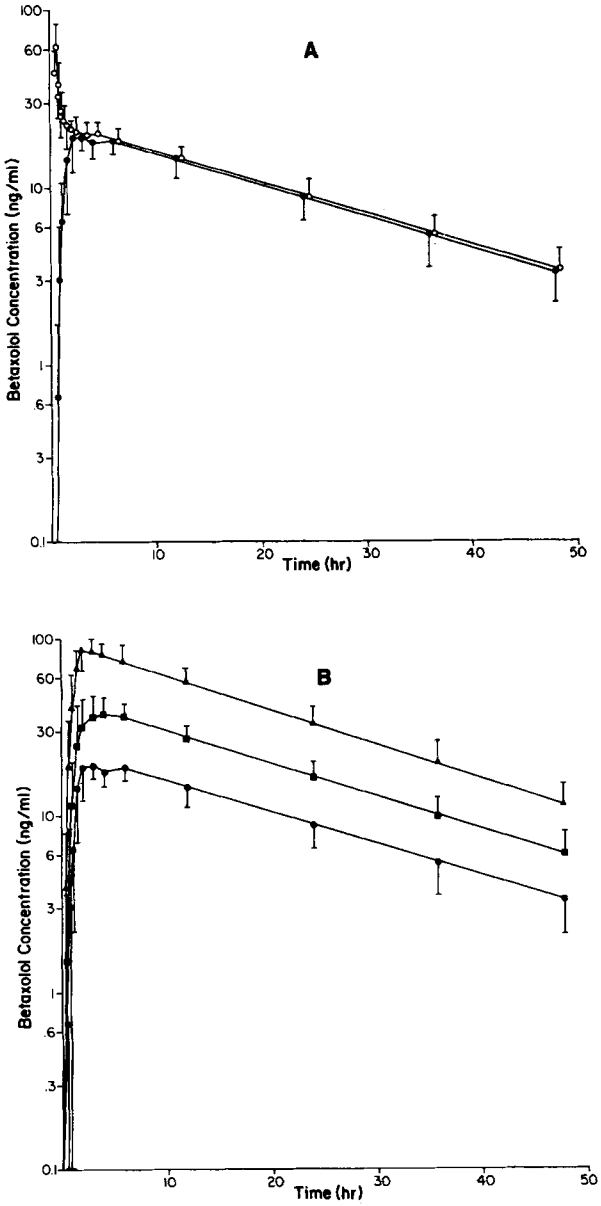

Figure 2—*Mean betaxolol concentration–time profiles. Panel A: iv dose of 10 mg (○); oral dose of 10 mg (●). Panel B: oral doses of 10 (●), 20 (■), and 40 mg (▲).*

intercompartmental clearance and central volume of distribution were available for only the 10 subjects whose data required a two-compartment open model for description. The mean clearance value obtained by compartmental analysis is in excellent agreement with the mean clearance value calculated from the AUC_∞ data by noncompartmental analysis (i.e., 3.42 ± 0.39 mL/kg min).

The noncompartmental (except for K_a) pharmacokinetic parameters for betaxolol are summarized in Table I. Normalized mean C_{max}, AUC_∞, and Xu_∞ values were in excellent agreement among the oral doses. Also, there was no evidence of a dose-related change in t_{max}l, t_{max}d, F, or CL_r. About 20% of the available dose was excreted unchanged in urine. The mean *ts* value increased slightly with dose, but the total change from the 10- to the 40-mg dose was only 7%. The mean lag time for the 40-mg doses was noticeably shorter than for the 10- or 20-mg doses, but was highly variable among individuals, as were the t_{max}l and t_{max}d values. On the other hand, the C_{max}, AUC_∞, *ts*, and F values exhibited low variability.

The K_a value, obtained by simultaneous fitting of the data for an oral dose and the iv dose, did not vary with dose. The harmonic mean absorption half-lives estimated in this manner were 1.37, 1.47, and 1.36 h for the 10-, 20-, and 40-mg doses, respectively.

Although normalized mean C_{max} values were in excellent agreement among doses (Table I), a statistically significant difference in normalized C_{max} values among the oral doses was detected. The Student-Newman-Keuls test indicated that this difference was between the 20- and 40-mg doses. A period effect was also noted for the C_{max} values with period 1 differing from periods 2, 3, and 4. However, the differences in C_{max} values (23.7 ± 3.1, 21.0 ± 5, 21.4 ± 4.7, and 20.7 ± 3.3 μg/L for periods 1, 2, 3, and 4, respectively) were small. Both the dose (Table I) and period differences noted were of a very low magnitude and of no clinical significance. A statistically significant dose-related difference in *ts* was found. The *ts* values after the iv and oral 10-mg doses were different from the *ts* value after the 40-mg oral dose. Again, the differences were obviously very small (Table I). As expected, given the somewhat incomplete bioavailability of betaxolol, the AUC_∞ and Xu_∞ values after the iv dose differed from these values after the oral doses.

Asymmetric 95% confidence intervals for the parameters for the 20- and 40-mg oral doses relative to the 10-mg oral dose are shown in Figure 3. The parameters most important clinically, C_{max}, *ts*, AUC_∞, and F, all exhibited very small confidence intervals that are well within the limits of ± 20%.

Table I—Pharmacokinetic Parameters for Betaxolol[a]

Parameter	Dose, mg			
	Intravenous	Oral		
	10	10	20	40
C_{max}, μg L^{-1} [b,c]	62.5 ± 19.7	21.6 ± 3.7	21.1 ± 3.7	22.5 ± 4.0
t_{max}l, min	—	145 ± 97	192 ± 75	142 ± 43
t_{max}d, min	—	184 ± 110	233 ± 91	170 ± 50
K_a, h^{-1}	—	0.505 ± 0.175	0.473 ± 0.239	0.510 ± 0.156
ts, h^{-1}	0.0415 ± 0.0050	0.0427 ± 0.0055	0.0437 ± 0.0048	0.0455 ± 0.0057
lag, min	—	39 ± 15	41 ± 20	28 ± 10
AUC_∞, μg h L^{-1} [b]	610 ± 122	540 ± 128	505 ± 112	524 ± 123
F, %	—	87.5 ± 7.9	82.3 ± 6.0	83.9 ± 6.6
Xu_∞, mg[b]	1.84 ± 0.72	1.55 ± 0.44	1.51 ± 0.45	1.45 ± 0.52
CL_r, mL min^{-1} kg^{-1}	0.700 ± 0.288	0.676 ± 0.215	0.690 ± 0.187	0.646 ± 0.221

[a] The results are expressed as means ± SD for 12 subjects. [b] Normalized to the 10-mg dose. [c] The C_{max} for the iv dose is included for informational purposes but is not appropriate for comparison with C_{max} for oral doses as a bioavailability parameter.

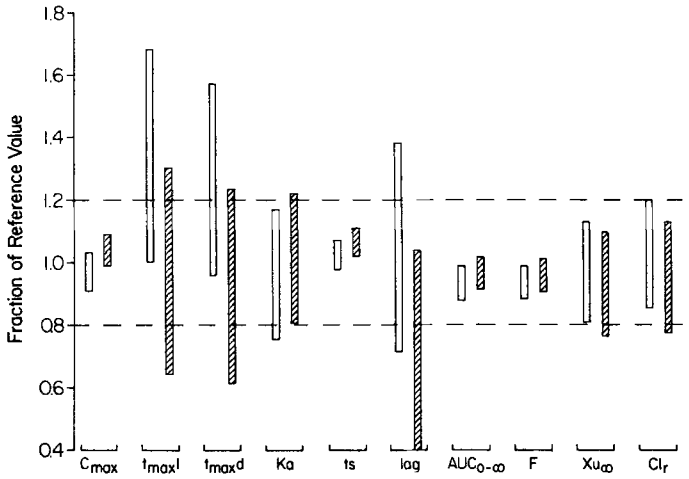

Figure 3—*The 95% confidence intervals for the ratios of pharmacokinetic parameters for the 20-* (□) *and 40-mg* (▨) *oral capsules relative to the 10-mg oral capsule.*

The parameters describing the rate of absorption, K_a, and renal excretion, Xu_∞ and CL_r, have confidence intervals that approximate the ± 20% range. On the other hand, the parameters that describe the delay prior to the beginning of absorption, lag, and those that describe the time of the maximum observed concentration, t_{max}l and t_{max}d, were variable and in some cases did not correspond well to the ± 20% range.

Discussion

Although statistically significant differences were found in C_{max}, *ts*, and AUC_∞ values among oral doses of 10, 20 and 40 mg, these differences have no clinical relevance. The differences in normalized C_{max} between the 20- and 40-mg doses is only 7%, the maximum difference in mean *ts* values was ~12%, and the difference in AUC_∞ between the 10- and 20-mg doses was only 7%. The use of analysis of variance is expected to yield differences when within-subject variability is low. In this case, the coefficient of variation within each subject is small, approximating that of the analytical procedure. Application of confidence intervals as well as inspection of the data support dose proportionality in all important parameters. These findings confirm previous studies that indicated dose proportionality upon single and multiple dosing.[4,14,17] The value of *F* found in this study (Table I) is in good agreement with those reported previously (75–89%).[2,4,5]

The primary route of betaxolol elimination is via nonrenal, presumably hepatic, processes yielding inactive or weakly active metabolites.[3,18] As found in this study, only a small fraction, ~18% of the absorbed dose, is excreted unchanged in the urine. The amount excreted unchanged was less following oral administration than after iv administration, as expected for the bioavailability of ~85% found in this study. The amount renally excreted was independent of dose. The low renal clearance is consistent with previous reports; however, refined dosage adjustments in hepatic or renal insufficiency of varying severity require additional study.[19,20]

Betaxolol differs from other beta-adrenoceptor blocking drugs in several respects.[21] It has long been believed that lipophilic beta-blockers have low, variable bioavailability because of moderate to high first-pass effects. Hence, iv doses are several times less than the usually prescribed oral doses. Propranolol and metoprolol are the most extensively studied examples.[19] Recently, development of beta-adrenergic antagonists has focused around water-soluble agents such as nadolol[22] and atenolol.[23] However, these agents have only moderately improved bioavailability (atenolol 64% and nadolol 30%).

The physicochemical (solubility) properties of betaxolol are similar to those of metoprolol.[21] However, different pharmacokinetic profiles between these two agents are clearly evident.[6,21] A plausible explanation for the high bioavailability of betaxolol is the presence of the cyclopropyl side chain. Through stearic hindrance of metabolic processes, first-pass extraction may be minimized. In the rat, increasing the molecular weight of this side chain by the substitution of a cyclobutyl group prolonged the elimination half-life.[3] This molecular modification may not only increase bioavailability but may also contribute to the low order of variability. Available data to date suggests that the metabolism of betaxolol is not perturbed by cimetidine[24] or markedly affected by hepatic insufficiency.[19,20] Unlike metoprolol, hydroxylase deficiency has little or no effect on the pharmacokinetics of betaxolol.[25]

In summary, the results of this study indicate that betaxolol is almost completely bioavailable following oral doses of 10–40 mg, the AUC_∞, Xu_∞, and C_{max} values are proportional to oral dose, and K_a, t_{max}, *F*, lag time, and CL_r values do not exhibit clinically significant changes with oral dose size. These findings clearly demonstrate that betaxolol exhibits excellent bioavailability and that its pharmacokinetic behavior is independent of dose.

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