Bioequivalence of a Highly Variable Drug: An Experience with Nadolol

Robert G. Buice,[1,3] Veerappan S. Subramanian,[1] Kenneth L. Duchin,[2] and Samuel Uko-Nne[1]

Received February 26, 1996; accepted April 11, 1996

Purpose. To assess the bioequivalence of nadolol 40mg and 160mg tablets (Zenith-Goldline Pharmaceuticals) using Corgard® 40mg and 160mg tablets (Bristol-Meyers Squibb) as reference products, to estimate the effect of food in the gastrointestinal tract on nadolol bioavailability, and to evaluate the effectiveness of standard pharmacokinetic metrics AUC_t, AUC_∞, and C_{max} in bioequivalence determinations.

Methods. Four bioequivalence studies were conducted as described in the FDA Guidance. Four additional studies of varying designs were conducted to establish bioequivalence of the 40mg tablet in terms of C_{max}.

Results. Fasted and food-effect studies of the 160mg tablet clearly established bioequivalence and revealed an unexpected reduction in nadolol bioavailability from test and reference products in the presence of food. The food-effect study of the 40mg tablet (80mg dose) revealed a similar reduction in bioavailability from each product. Fasted studies of the 40mg tablet (80mg dose) established bioequivalence in terms of AUC_t and AUC_∞. However, C_{max} criteria proved extremely difficult to meet in the initial 40mg fasted study because of the large variability, leading to additional studies and ultimately requiring an unreasonable number of subjects.

Conclusions. Final results clearly established bioequivalence of both strengths and characterized an unexpected food effect which did not appear to be formulation-related. However, the C_{max} of nadolol is only slightly sensitive to absorption rate and the relatively large variability of C_{max} reduces its effectiveness as a bioequivalence metric. Findings suggest that bioequivalence criteria for highly variable drugs should be reconsidered.

KEY WORDS: nadolol; pharmacokinetics; bioequivalence; variability.

INTRODUCTION

Nadolol, a nonselective β-adrenergic blocking agent which is structurally and pharmacologically similar to propranolol, decreases blood pressure at rest and during stress (1). The precise mechanism of action has not been established, although it has been postulated that agents of this class reduce blood pressure by decreasing cardiac output and sympathetic outflow from the CNS and/or by suppressing renin release (2).

Through its myocardial β-adrenergic blocking action, nadolol decreases exercise-induced increase in double product (heart rate X systolic blood pressure) (3). It also slows conduction through the atrioventricular (AV) node and decreases myocardial automaticity (firing rate of SA node) by β-adrenergic blockade. It has no membrane-stabilizing effect on the heart nor does it exhibit intrinsic sympathomimetic activity (4).

[1] Scientific Operations, Zenith-Goldline Pharmaceuticals, Northvale, New Jersey.

[2] Clinical Pharmacology, Baker-Norton Pharmaceuticals, Miami, Florida.

[3] To whom correspondence should be addressed.

Nadolol in the plasma is 18 to 22% bound to proteins (5) and the volume of distribution is approximately 2L/kg (6). As nadolol does not undergo biotransformation, clearance is predominantly by renal excretion of unchanged drug (7). The total body clearance of nadolol equals creatinine clearance (8). In patients with normal renal function, the (mean ± sd) plasma half-life of nadolol is 10.40 ± 2.96 hr following a single 80mg dose and 11.60 ± 4.80 at steady-state (9). Pharmacokinetic nonlinearity has been suggested following multiple dosing of 80mg/day (9), although one single-dose study indicates linear dose-proportionality through 120mg (10). Gastrointestinal absorption following oral administration is relatively low and variable, ranging from 27% of a single dose to 39% following multiple doses (5). Peak plasma concentrations are observed within 2 to 4hr after oral administration of 80mg, although peaks as early as 1hr have been reported (5). Previous findings suggest that the presence of food in the GI tract does not affect the rate or extent of absorption (11).

Present studies assess the bioequivalence of nadolol 40mg and 160mg tablets (Zenith-Goldline), using Corgard® 40mg and 160mg tablets (Bristol-Meyers Squibb) as reference products. The effect of the presence of food in the gastrointestinal tract is also considered.

MATERIALS AND METHODS

Products

Nadolol is available as 160, 120, 80, 40, and 20mg tablets. Formulation proportionality exists over the 160, 120, and 80mg strengths and over the 40 and 20mg strengths. The test product was formulated to match the reference at each strength.

Study Designs

The first four studies were conducted to meet the requirements specified in the FDA Guidance(11). Accordingly, a fasted and food-effect study was conducted at 160mg in support of the upper strengths and at 80mg (2 × 40mg tablets) in support of the lower strengths. These studies were designed as follows:

Study 1 A single-dose (160mg tablet), randomized, two-way crossover completing with 35 subjects dosed in 2 groups under *fasted* conditions.

Study 2 A single-dose (160mg tablet), randomized, three-way crossover *food-effect* study completing with 17 subjects.

Study 3 A single-dose (2 × 40mg tablets), randomized, two-way crossover completing with 35 subjects under *fasted* conditions.

Study 4 A single-dose (2 × 40mg tablets), randomized, three-way crossover *food-effect* study completing with 17 subjects.

Four additional studies were designed in attempts to demonstrate bioequivalence despite the highly variable nature of the nadolol C_{max}:

Study 5 A single-dose (2 × 40mg tablets), randomized, two-way crossover completing with 36 subjects under *fed* conditions.

0724-8741/96/0700-1109$09.50/0

Study 6 A single-dose (2 × 40mg tablets), randomized, two-treatment, four-period *replicate* completing with 19 subjects under *fasted* conditions.

Study 7 A single-dose (4 × 40mg tablets), randomized, two-way crossover completing with 57 subjects dosed in 2 groups under *fasted* conditions.

Study 8 A single-dose (2 × 40mg tablets), randomized, two-way crossover completing with 58 subjects dosed in 2 groups under *fasted* conditions.

Subjects

Adult male subjects between the ages of 19 and 50 yr were used for all studies. Each subject was within ±15% of the normal weight range defined by the Metropolitan Life Insurance Company Statistical Bulletin (1983) and in good health as indicated by medical history, physical examination, clinical laboratory tests, ECG, and chest X-ray.

Study Design and Clinical Procedures

Fasted studies were conducted using single-dose, open-label, randomized, 2-way crossover designs with each subject receiving the indicated oral dose on 2 occasions, separated by a 7-day washout period. Subjects were admitted to the Clinical Study Unit the evening prior to dosing and were fasted overnight through 4 hr postdose. A single fed study was conducted using a single-dose, open-label, randomized, 2-way crossover design with each subject receiving a 2 × 40mg oral dose on 2 occasions, separated by a 7-day washout period. Fed study subjects were admitted to the Clinical Study Unit the evening prior to dosing, were fasted overnight, and received a standard meal 30min prior to dosing. The meal consisted of one buttered English muffin, one fried egg, one slice of American cheese, one slice of Canadian bacon, one serving of hash brown potatoes, 180ml orange juice, and 240ml whole milk.

Food-effect studies were conducted using single-dose, open-label, randomized, 3-way crossover designs comparing Test-Fed with Reference-Fed and Test-Fed with Test-Fasted. Each subject received a 160mg or 2 × 40mg oral dose on 3 occasions, each separated by a 7-day washout period. Subjects assigned to a fasted treatment were admitted to the Clinical Study Unit the evening prior to dosing and were fasted overnight through 4 hr postdose. Subjects assigned to a fed treatment were admitted to the Clinical Study Unit the evening prior to dosing, were fasted overnight, and received the previously-described standard meal 30min prior to dosing.

Beginning at 8am on each dosing day, the dose was administered to each subject followed immediately by 240ml water. All subjects remained seated or ambulatory until receiving lunch 4hr post dosing. They were not permitted to be in the supine position during the first 8 hr. Smoking was not permitted from 1hr predose to 4hr postdose. Subjects were constantly observed for adverse events and were questioned about the occurrence of any medical problem.

Sample Collection and Treatment

Samples of venous blood (15ml) were obtained using heparinized Vacutainers® pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, and 60 hr post dose. Initial studies included a 72 hr sample. Any sampling time which deviated from the schedule by more than 5% through 10hr or by more than 0.5hr from 12–18 hr was recorded. Samples were collected under gold fluorescent lights, centrifuged at 10°C and 2500rpm for 20min, and the plasma was stored at −10°C prior to bioanalysis.

Bioanalytical Method

Plasma nadolol concentrations were measured by reverse-phase high performance liquid chromatography with fluorescence detection. Nadolol and internal standard were recovered from the plasma matrix by liquid-liquid extraction into n-butyl Cl/n-butanol and then into hydrochloric acid. Extracted samples were chromatographed on a C-8 column (5μ, 25cm × 4.6mm) using acetonitrile/ammonium acetate buffer as the mobile phase. Recovery of nadolol and internal standard from the plasma matrix were 105 and 76.5%, respectively. Linearity was achieved between the limit of quantitation (5.0 ng/ml) and 750ng/ml. Intra-day precision ranged from 1.70% at 500 ng/ml to 3.67% at 5 ng/ml. Intra-day accuracy ranged from 98.1 to 103%. Freeze-thaw stability was adequate.

Pharmacokinetic Analysis

Plasma drug concentration-time course data were analyzed in terms of conventional bioequivalence metrics which included the peak plasma concentration (C_{max}), the area under the curve from zero to the last measurable concentration (AUC_t), and the area under the curve from zero to infinity (AUC_∞). In addition, the ratio of C_{max}/AUC_∞ and the time from dosing to the peak concentration (t_{max}) were determined. AUC_t was estimated using the trapezoidal rule and AUC_∞ was calculated as:

$$AUC_\infty = AUC_t + \frac{C_t}{\lambda}$$

C_t is the last measurable concentration and λ is the negative slope of the final ln-linear phase of the plasma concentration time-course curve. C_{max} and t_{max} were determined directly from the plotted data.

Statistical Analysis

Analysis of Variance (ANOVA) using a type III sum of squares was used to determine significant differences ($\alpha = 0.05$). Least squares means were computed using a general linear model with effects specifically required for each study design as described below:

Study 1 Group, sequence, group*sequence, subject(group* sequence), phase(group), treatment, and group* treatment.

Study 2 Sequence, subject(sequence), phase, and treatment.

Study 3 Sequence, subject(sequence), phase, and treatment.

Study 4 Sequence, subject(sequence), phase, and treatment.

Study 5 Sequence, subject(sequence), phase, and treatment.

Study 6 Sequence, subject(sequence), phase, treatment, phase*treatment, and carry-over.

Study 7 Group, sequence, group*sequence, subject(group* sequence), phase(group), treatment, and group* treatment.

Study 8 Group, sequence, group*sequence, subject(group* sequence), phase(group), treatment, and group* treatment.

Table 1. Area Under the Curve from Zero to the Final Measurable Concentration (AUC_t)

FASTED AND FED STUDIES

Study	Product & Dose	Design	Test Mean	Ref Mean	LSM Ratio	90% CI	Within-Subject CV (%)
1	1 × 160mg	2 × 2 Fasted N = 35	5547	5508	1.00	0.91 to 1.12	25.9
3	2 × 40mg	2 × 2 Fasted N = 35	1696	1835	0.92	0.84 to 1.02	24.4
5	2 × 40mg	2 × 2 **Fed** N = 36	1293	1312	0.99	0.93 to 1.04	13.7
6	2 × 40mg	**2 × 4** Fasted N = 19	2068	2039	1.01	0.93 to 1.11	23.4
7	**4 × 40mg**	2 × 2 Fasted **N = 57**	4652	4523	1.03	0.96 to 1.10	21.5
8	**2 × 40mg**	2 × 2 Fasted **N = 58**	2075	2056	0.97	0.88 to 1.08	32.7

FOOD-EFFECT STUDIES

Study	Product & Dose	Design		Test Mean	Ref Mean	LSM Ratio	Within-Subject CV (%)
2	1 × 160mg	3 × 3 N = 17	Test Fed vs Ref Fed	3106	3228	1.02	25.3
		3 × 3 N = 17	Test Fed vs Test Fast	3106	4072	0.79	
4	2 × 40mg	3 × 3 N = 12	Test Fed vs Ref Fed	1240	1226	1.02	25.2
		3 × 3 N = 12	Test Fed vs Test Fast	1240	1680	0.76	

The power of each study to detect a 20% difference as significant ($\alpha = 0.05$) was calculated using the sample estimates and significance level of the central Student's t-distribution.

Confidence intervals (90%) were calculated around ratios of least squares means derived from ln-transformed data using the standard error of the estimate of the formulation difference from the ANOVA. Results of all FASTED studies and one two-way crossover study under FED conditions were evaluated using 90% confidence intervals. FOOD-EFFECT study results were assessed by direct comparison of test/reference least squares means ratios.

RESULTS

Results of all studies are summarized in Tables 1–4. All pharmacokinetic metrics clearly indicated that the 160mg tablet is bioequivalent to the reference. Moreover, for both the 40 and 160mg strengths the presence of food significantly reduced the LSM ratio (test-fed/test-fasted) of each metric, although the LSM ratio (test-fed/reference-fed) approximated unity. Within-subject variabilities at the 40 and 160mg strengths suggested that nadolol is a relatively variable drug, indeed highly variable for C_{max}.

The initial fasted study supporting the 40mg strength (Study 3) suggested bioequivalence in terms of AUC_t and AUC_∞, but for C_{max} the 90% confidence intervals (0.77–1.03) fell slightly below acceptable limits (0.80–1.25). Again, within-subject variability indicated a moderately variable AUC_t and AUC_∞ (Within-Subject CV = 24.4% and 24.2%, respectively) and a highly variable C_{max} (Within-Subject CV = 35.7%).

A true test of equivalence in terms of C_{max} required that the issue of variability be addressed. Because the presence of food tends to reduce variability, another study (Study 5) was conducted as a two-way crossover under fed conditions. Variability was indeed reduced (Within-Subject CV for AUC_t,

Table 2. Area Under the Curve from the Final Measurable Concentration to Infinity (AUC_∞)

FASTED AND FED STUDIES

Study	Product & Dose	Design	Test Mean	Ref Mean	LSM Ratio	90% CI	Within-Subject CV (%)
1	1 × 160mg	2 × 2 Fasted N = 35	5727	5676	1.01	0.91 to 1.12	25.2
3	2 × 40mg	2 × 2 Fasted N = 35	1910	2004	0.95	0.86 to 1.05	24.2
5	2 × 40mg	2 × 2 **Fed** N = 36	1509	1489	1.01	0.96 to 1.07	13.0
6	2 × 40mg	**2 × 4** Fasted N = 19	2278	2275	1.00	0.92 to 1.09	22.2
7	**4 × 40 mg**	2 × 2 Fasted **N = 57**	4925	4803	1.03	0.96 to 1.10	20.9
8	**2 × 40 mg**	2 × 2 Fasted **N = 58**	2266	2249	0.98	0.89 to 1.07	29.3

FOOD-EFFECT STUDIES

Study	Product & Dose	Design		Test Mean	Ref Mean	LSM Ratio	Within-Subject CV (%)
2	1 × 160mg	3 × 3 N = 17	Test Fed vs Ref Fed	3505	3651	1.02	23.7
		3 × 3 N = 17	Test Fed vs Test Fast	3505	4376	0.83	
4	2 × 40mg	3 × 3 N = 12	Test Fed vs Ref Fed	1424	1393	1.04	23.1
		3 × 3 N = 12	Test Fed vs Test Fast	1424	1854	0.79	

AUC_∞, and C_{max} = 13.7, 13.0, and 13.6%, respectively) and bioequivalence was again clearly demonstrated for all 3 standard metrics.

Findings at this point clearly indicated that the test product was bioequivalent to the reference but that C_{max} criteria were difficult to meet using the standard two-way crossover fasted study because of the large variability. However, existing regulatory policies require the demonstration of bioequivalence under fasted conditions and with such a highly variable C_{max} the standard fasted study design would require an unusually large number of subjects. In an attempt to overcome this problem a four-period replicate study (Study 6), which required fewer subjects, was conducted under fasted conditions. This study completed with 19 subjects and results yet again suggested bioequivalence in terms of AUC_t and AUC_∞. However, for C_{max} the 90% confidence intervals (0.96–1.26) slightly exceeded acceptable limits (0.80–1.25). Again, within-subject variability indicated a moderately variable AUC_t and AUC_∞ (Within-Subject CV = 23.4% and 22.2%, respectively) and a highly variable C_{max} (Within-Subject CV = 35.0%).

All findings indicated that the demonstration of bioequivalence would require either a reduction in the variability of C_{max} or an increase in the power of the study to demonstrate bioequivalence despite such large variability. In the next study (Study 7) the dose was doubled (4 × 40mg tablets) to reduce potential bioanalytical variability and the number of subjects was increased (60 entered/57 completed) to optimize statistical power. Results of this study indicated that the product was bioequivalence in terms of all standard metrics. Because previous studies were conducted using a dose of 80mg (2 × 40mg tablets) and pharmacokinetic linearity had not been established at doses exceeding 120mg(10), the study was repeated (Study 8) (60 entered/58 completed) to demonstrate bioequivalence at the previously-used dose of 80mg (2 × 40mg tablets). Again, bioequivalence was clearly demonstrated for all metrics.

Table 3. Maximum Concentration in the Plasma (C_{max})

FASTED AND FED STUDIES

Study	Product & Dose	Design	Test Mean	Ref Mean	LSM Ratio	90% CI	Within-Subject CV (%)
1	1 × 160mg	2 × 2 Fasted N = 35	484	510	0.95	0.82 to 1.09	**34.6**
3	2 × 40mg	2 × 2 Fasted N = 35	125	140	0.89	**0.77 to 1.03**	**35.7**
5	2 × 40mg	2 × 2 **Fed** N = 36	82	80.3	1.02	0.97 to 1.08	13.6
6	2 × 40mg	**2 × 4** Fasted N = 19	162	147	1.10	**0.96 to 1.26**	**35**
7	**4 × 40mg**	2 × 2 Fasted **N = 57**	414	397	1.04	0.94 to 1.15	**31.8**
8	**2 × 40mg**	2 × 2 Fasted **N = 58**	181.0	173.1	1.01	0.87 to 1.17	47.7

FOOD-EFFECT STUDIES

Study	Product & Dose	Design		Test Mean	Ref Mean	LSM Ratio	Within-Subject CV (%)
2	1 × 160mg	3 × 3 N = 17	Test Fed vs Ref Fed	200.8	218.4	0.93	34.2
		3 × 3 N = 17	Test Fed vs Test Fast	200.8	358.8	0.58	
4	2 × 40mg	3 × 3 N = 12	Test Fed vs Ref Fed	78.0	77.5	1.00	33.0
		3 × 3 N = 12	Test Fed vs Test Fast	78.0	117.0	0.67	

DISCUSSION

It is clear from present data, fasted and fed, that the test and reference products are bioequivalent. The presence of food in the gastrointestinal tract reduced nadolol bioavailability. This food effect had not been previously reported (11) and was independent of formulation.

While none of the present findings suggested bioINequivalence, results of this series of studies tend to question existing bioequivalence requirements, especially the value of the C_{max} as an index of absorption rate and the rigid 90% confidence interval criteria which are applied without regard to variability. The establishment of bioequivalence in terms of rate and extent of gastrointestinal absorption is a standard requirement of the U.S. Food and Drug Administration. Further, it is conventional to use C_{max} as an index of rate and AUC as an index of extent. C_{max}/AUC has been proposed as an alternate metric to be used as an index of rate. Indeed, a previous report (12) suggested that the C_{max}/AUC of nicardipine is much more rate-sensitive than C_{max} and is less variable than all other metrics. Obviously, the sensitivity of C_{max} or C_{max}/AUC to rate would depend upon the relationship of k_a to K and this would have to be determined for each drug. Simulations of the nadolol C_{max} and C_{max}/AUC *vs* the absorption rate constant (k_a), based upon nadolol population pharmacokinetic parameter values (Figure 1), suggested that for this drug the C_{max} might be slightly more rate-sensitive than C_{max}/AUC, especially in the region of the nadolol k_a. However, neither metric is sufficiently rate-sensitive to act as an index of nadolol absorption rate.

Thus, the value of C_{max} as an index of nadolol absorption rate appears to be minimal at best. However, despite the lack of sensitivity of the nadolol C_{max} to absorption rate, regulatory policies mandate that this metric be analyzed for the establishment of bioequivalence. Moreover, the standard 90% Confidence Interval criteria (0.80–1.25) are required, despite the

Table 4. Maximum Concentration in the Plasma Divided by the Area Under the Curve from the Final Measurable Concentration to Infinity ($C_{max}/AUC_{0-\infty}$)

FED AND FASTED STUDIES							
Study	Product & Dose	Design	Test Mean	Ref Mean	LSM Ratio	90% CI	Within-Subject CV (%)
1	1 × 160mg	2 × 2 Fasted N = 35	0.0845	0.0899	0.94	0.88 to 1.01	16.7
3	2 × 40mg	2 × 2 Fasted N = 35	0.0660	0.0699	0.94	0.86 to 1.03	21.5
5	2 × 40mg	2 × 2 **Fed** N = 36	0.0544	0.0540	1.01	0.95 to 1.06	13
6	2 × 40mg	**2 × 4** Fasted N = 19	0.0713	0.0647	1.10	1.02 to 1.19	20.1
7	**4 × 40mg**	2 × 2 Fasted **N = 57**	0.0841	0.0827	1.02	0.96 to 1.08	19
8	**2 × 40mg**	2 × 2 Fasted **N = 58**	0.077	0.074	1.04	0.95 to 1.12	26.3

extremely large variability of the nadolol C_{max}. Accordingly, despite the clearly-established bioequivalence of the test and reference products, standard criteria were extremely difficult to meet. Thus, 4 unnecessary studies (Studies 5, 6, 7, and 8) involving 170 extra subjects were conducted, not to scientifically establish bioequivalence, but to meet standardized regulatory criteria involving a metric, C_{max}, which is essentially useless in its stated role as an index of absorption rate and much too variable to provide any meaningful assessment of bioequivalence.

The enormous cost of product development adds to the overall cost of health care and this is ultimately passed on

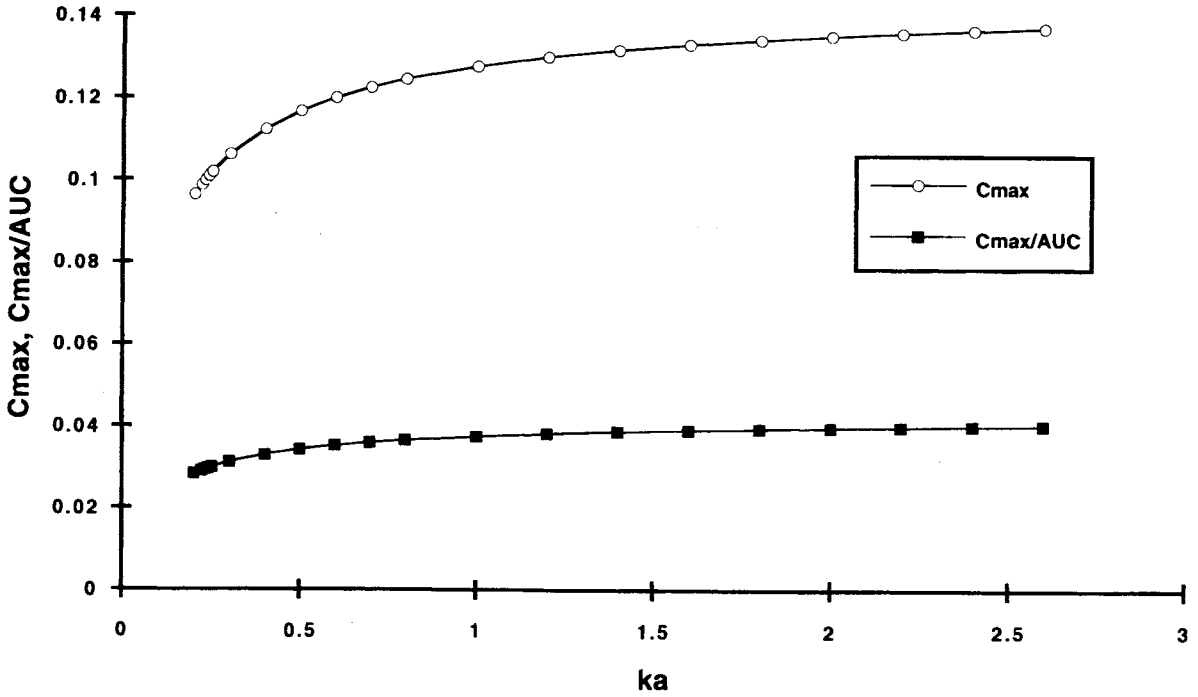

Fig. 1. Simulated C_{max} (ng/ml) and C_{max}/AUC (hr^{-1}) values at varying absorption rate constants, k_a (hr^{-1}). The k_a of nadolol ranges from 0.75 to 2.0hr^{-1}, corresponding to the observed t_{max} range of 2 to 4 hr.

to the consumer. Unreasonable bioequivalence requirements, necessitating excess studies can only increase this cost. Overall findings from this series of studies suggest that no single metric is adequate for every drug and that the absorption rate metric required for bioequivalence should be decided on a case by case basis. Findings further suggest that the 90% confidence interval criteria should be adjusted for highly variable drugs.

REFERENCES

1. A. H. Jiminez, G. H. Tofler, X. Chen, M. E. Stubbs, H. S. Solomon, and J. E. Muller. Effects of nadolol on hemodynamic and hemostatic responses to potential mental and physical triggers of myocardial infarction in subjects with mild systemic hypertension. *Amer. J. Cardiol.* **72**:47–52 (1993).
2. J. Bonelli, W. Waldhausl, D. Magometschnigg, J. Schwarzmeier, A. Korn, and G. Hitzenberger. Effects of exercise and of prolonged oral administration of propranolol on hemodynamic variables, plasma renin concentration, plasma aldosterone, and cAMP. *Europ. J. Clin. Invest.* **7**:337–343 (1977).
3. R. A. Vukovich, J. E. Foley, B. Brown, D. A. Willard, M. Buckley, D. O'Kelly, D. Fitzgerald, W. Tormey, and A. Darragh. Effects of β-blockers on exercise double product. *Brit. J. Clin. Pharm.* **7**:167S–172S (1979).
4. K. L. Duchin, R. A. Vukovich, L. G. Dennick, J. T. Groel, and D. A. Willard, Effects of nadolol β-blockade on blood pressure in hypertension. *Clin. Pharmacol. Therap.* **27**:57–63 (1980).
5. J. Dreyfuss, D. L. Griffith, S. M. Singvhi, J. M. Shaw, J. J. Ross, R. A. Vukovich, and D. A. Willard. Pharmacokinetics of nadolol, a beta-receptor antagonist: Administration of single and multiple-dose regimens to hypertensive patients. *J. Clin. Pharmacol.* **19**:712–720 (1979).
6. R. A. Morrison, S. M. Singvi, W. A. Creasey, and D. A. Willard. Dose proportionality of nadolol pharmacokinetics after intravenous administration in healthy subjects. *Eur. J. Clin. Pharmacol.* **33**:625–628 (1988).
7. D. G. McDevitt. Comparison of pharmacokinetic properties of beta-adrenoceptor blocking agents. *Eur. Heart. J.* **8**:9–14 (1987).
8. J. Herrera, R. A. Vukovich, and D. L. Griffith. Elimination of nadolol in patients with renal impairment. *Br. J. Clin. Pharmacol.* **7**:227S–231S (1979).
9. J. J. Krukemeyer, H. Buodoulas, P. F. Binkley, and J. J. Lima. Comparison of single-dose and steady-state nadolol plasma concentrations. *Pharm. Res.* **7**:953–956 (1990).
10. M. Schafer-Korting, N. Bach, H. Knauf, and E. Mutschler. Pharmacokinetics of nadolol in healthy subjects. *Eur. J. Clin. Pharmacol.* **26**:125–127 (1984).
11. *GUIDANCE,* Nadolol Tablets: In Vivo Bioequivalence and In Vitro Dissolution, Division of Bioequivalence, Office of Generic Drugs, U. S. Food and Drug Administration, May 16, 1992.
12. R. G. Buice, V. Subramanian, and E. Lane. Bioequivalence of two orally-administered nicardipine products. *Biopharm. Drug. Disp. in press.*