Steady-State Bioavailability and Day-to-Day Variability of a Multiple-Unit (CR/ZOK) and a Single-Unit (OROS) Delivery System of Metoprolol After Once-Daily Dosing

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Steady-state bioavailability and day-to-day variability of plasma levels were evaluated in 18 healthy male subjects in a crossover study of multiple once-daily administration of two novel oral drug delivery systems of metoprolol and an immediate-release tablet (100 mg metoprolol tartrate). Data were collected over two consecutive 24-hr dosing intervals on treatment days 6 and 7. The two extended-release formulations investigated were metoprolol CR/ZOK (95 mg metoprolol succinate), a multiple-unit system consisting of several hundred membrane-coated delivery units, and metoprolol OROS (95 mg metoprolol fumarate), a single-unit osmotic delivery system. The extended drug release and absorption observed after administration of metoprolol CR/ZOK and metoprolol OROS resulted in similar steady-state plasma concentrations after once-daily dosing. Compared to the immediate-release tablet, they produced considerably lower plasma peaks, three- to fourfold higher trough concentrations, 8–9 hr longer mean residence times, and 20% lower relative bioavailability. Moreover, the two once-daily metoprolol products were found bioequivalent in C_{max} and AUC based on 90% confidence intervals for the mean ratio CR/OROS. Repeated plasma concentration measurements on two consecutive 24-hr periods suggested that all three metoprolol treatments produced reproducible and consistent plasma concentrations from day to day at steady state. Assessment of day-to-day variability, however, resulted in significantly lower variation in AUC for the multiple-unit CR/ZOK formulation compared to the single-unit OROS tablet. These results imply that there may be formulation-related differences in the *in vivo* behavior of the two products despite their being bioequivalent in extent and rate of absorption.

KEY WORDS: extended-release metoprolol; steady-state bioavailability; day-to-day variability.

INTRODUCTION

Metoprolol is a β_1-selective adrenoceptor antagonist with wide therapeutic usage, particularly in the management of hypertension and ischaemic heart disease. The drug's relatively short elimination half-life, 3 to 4 hr, has led to the development of various extended-release formulations, aimed at providing consistent and continuous plasma concentrations and β_1 blockade throughout the dosing interval with convenient once-daily dosing. Earlier formulations of the matrix type (e.g., Betaloc SA, Lopressor SR) have failed, at least partially, in this respect since they release the drug too rapidly to provide continuous 24-hr β_1 blockade after once-daily administration (1).

Two novel delivery systems, denoted metoprolol CR/ZOK and metoprolol OROS, release the drug more slowly and at a relatively constant rate over most of the 24-hr dosing interval. Both these preparations were shown to produce sustained and consistent steady-state plasma concentrations and β_1 blockade after once-daily dosing over a wide dosage range (2–5). They also appear to be more β_1 selective than conventional tablets of metoprolol and atenolol because of their consistently low plasma concentrations over the dosing interval (6,7).

Both metoprolol CR and metoprolol OROS are extended-release formulations of the reservoir type, consisting of a drug core surrounded by a release-controlling polymeric membrane. However, they represent two different formulation principles since the CR is a multiple-unit system (disintegrating tablet) containing hundreds of individually coated pellets (8), whereas the OROS is an osmotically controlled nondisintegrating single-unit tablet (9).

This study was performed to compare the bioavailability properties of these two metoprolol extended-release formulations and conventional metoprolol tablets after multiple once-daily dosing. The objective was also to assess the day-to-day variability of the three metoprolol treatments by taking replicate samples during two consecutive dosing intervals at steady state.

MATERIALS AND METHODS

Subjects and Ethical Considerations

Eighteen healthy young male Caucasians aged 21–33 years (mean, 25 years) and weighing 67–86 kg (mean, 77 kg) volunteered for the study. Every subject was judged healthy based on his medical background, a prestudy physical examination, ECG, and a clinical laboratory investigation including hematology, blood serum analysis, and urinalysis. The subjects were informed verbally and in writing about the nature of the study and all gave written informed consent before enrollment. The study was conducted in accordance with the Declaration of Helsinki and the study protocol was approved by the local Ethics Committee of Gothenburg University and by the Swedish Health Authorities (Medical Products Agency, Uppsala).

Study Design and Procedures

The study was of a three-way crossover randomized (Latin square, balanced for residual effects) design, with repeated measurements on 2 consecutive days (6 and 7) at steady state. Each of the three study periods consisted of 7 treatment days and was separated by drug-free intervals of 7 days.

On each day, subjects received one of the three medi-

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cations on an empty stomach (after at least a 10-hr fast) in the morning together with 200 ml of tap water. On days 1, 5, 6, and 7, drug intake was supervised by the laboratory staff, and standardized food and beverages were served at specified times, 0.5 (light breakfast), 3, 6, 10, and 14 hr after drug administration. On study days 2, 3, and 4, no measurements were made at the laboratory, and the subjects were allowed to take their medication at home in a similarly standardized manner. No alcohol or other drugs were permitted for the duration of the study and the use of tobacco was not allowed during the study days at the laboratory.

Study Medications

Metoprolol CR/ZOK (CR), AB Astra, lot No. NM 229, is a multiple-unit formulation containing 95 mg of metoprolol succinate as coated pellets in a disintegrating tablet (8).

Metoprolol OROS (OROS), Ciba-Geigy, lot No. L 001, contains 95 mg of metoprolol fumarate in a nondisintegrating single-unit tablet coated with a semipermeable membrane (9). This formulation is described as the elementary osmotic pump (10).

The conventional immediate-release tablet (CT), AB Astra, lot. No. MI 497, contained 100 mg of metoprolol tartrate. These quantities of the three salts are dose equivalent with respect to the metoprolol base. All study medications were commercial compositions.

Sampling and Analysis

Five-milliliter venous blood samples for analysis of metoprolol were collected before drug administration on days 1 (blank), 5, 6, 7, and 8 (24 hr after last dose). Further blood samples were collected via an indwelling catheter at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, and 14 hr after dosing on days 6 and 7. Samples were also taken on day 8 at 27 and 30 hr after last dose.

The blood samples were collected into heparinized tubes and centrifuged. The plasma was decanted and kept frozen at −20°C until analysis. Metoprolol plasma concentrations were measured by gas chromatography with electron-capture detection (11). Validation of the method was performed during the course of the study and the lowest determinable concentration of the assay was set to 10 n*M* ($SD_{rel} \leq 15\%$).

A blank urine sample was collected on day 1 prior to drug administration. After emptying the bladder before dosing on day 6, all urine was collected and pooled over each of the 24-hr dosing intervals on days 6 and 7. An aliquot of 5–8 ml was taken and kept frozen at −20°C until analysis. The 24-hr urine samples were analyzed for metoprolol and two of the (three) major urinary metabolites; H 117/04, an inactive aliphatic carboxylic acid, and H 119/66, the partially active α-hydroxy (4-OH) metoprolol (12). The three compounds were determined by column liquid chromatography and fluorimetric detection (13). The minimum determinable concentration of the assay was 1 μ*M* (metoprolol), 2 μ*M* (H 117/04), and 1 μ*M* (H 119/66) of urine, respectively.

The subjects were asked to collect the tablet residue from feces during treatment with the OROS formulation whenever possible. These tablets were analyzed for remaining drug (metoprolol fumarate) by liquid chromatography.

In vitro release–time profiles were established for the CR and OROS formulations under various testing conditions (see Table I) using USP dissolution apparatus No. 2, 500 ml of test medium at 37°C, and UV-spectrophotometric determination of metoprolol at 274 nm. Statistical moment analysis was used to determine the mean time for *in vitro* dissolution of these profiles (14).

Calculations and Statistics

Attainment of steady state was examined in each treatment period by stepwise *t*-test comparisons between the 24-hr plasma concentration on day 8 and the corresponding (predose) values on days 5, 6, and 7. The variances for these tests were estimated by the mean squared error from an analysis of variance (ANOVA) performed on each difference.

The pharmacokinetic variables estimated for each subject and treatment on days 6 and 7 were C_{max}, t_{max}, MRT (mean residence time), AUC (area under the curve from 0 to 24 hr), and the plasma elimination half-life (only CT). The AUC was estimated by the linear trapezoidal rule, either alone (CR and OROS) or in combination with the log-trapezoidal rule (CT). The logarithmic method was applied for the interval 14–24 hr postdosing of CT. Further, the percentage peak-trough fluctuation of plasma levels over the dosing interval was calculated according to the formula:

$$100 \cdot [(C_{max} - C_{min})/(AUC/\tau)]$$

where τ = 24 hr. C_{min} was defined as the mean of the predose (0-hr) plasma concentrations representing steady state according to the analysis above.

The day-to-day variation in bioavailability (expressed as percentage) was determined as the absolute difference of AUC values (day 6–day 7) divided by the estimated mean AUC for these days.

Treatment differences for AUC, C_{max}, MRT, and percentage fluctuation were tested by means of a multiplicative ANOVA model, separating the effects related to subject,

Table I. Mean Time (Hours) for *in Vitro* Dissolution of Metoprolol Succinate and Metoprolol Fumarate from CR and OROS, Respectively[a]

	Dissolution conditions (pH of medium[b] and paddle speed)						
Formulation	pH 1.2/50 rpm	pH 1.2/100 rpm	pH 2.0/100 rpm	pH 4.0/100 rpm	pH 5.5/100 rpm	pH 6.8/50 rpm	pH 6.8/100 rpm
CR	8.55	8.63	8.97	8.71	8.19	8.44	8.70
OROS	7.26	7.10	8.57	8.56	8.12	8.08	7.93

[a] Values are based on mean cumulative dissolution–time curves. Method: USP apparatus No. 2; 500 ml test medium at 37°C; n = 6 tablets.
[b] pH 1.2, simulated gastric juice USP without enzymes; pH 2.0–6.8, phosphate buffer solutions, ionic strength 0.1.

period, and drug treatment. For C_{min}, a corresponding additive model was applied. The residual error was used in the pairwise comparisons when testing for significant differences ($P < 0.05$) and establishing 90% confidence intervals for the treatment ratios. The analysis was based on the mean observation of the two treatment days.

The same ANOVA model was applied in the analysis of treatment differences in the day-to-day variability of AUC. These tests were based on the absolute difference of AUC values obtained on days 6 and 7.

The difference in t_{max} between CR and OROS was tested nonparametrically as described by Hauschke *et al.* (15). The result is given as a distribution-free 90% confidence interval.

RESULTS AND DISCUSSION

All subjects completed the study periods according to the protocol. The study medications were generally very well tolerated by the subjects. Most of the 19 adverse events reported in total were mild and of a general nature (e.g., headache and tiredness), and there were no apparent differences among the three metoprolol treatments regarding adverse events.

In Vitro Dissolution

Both metoprolol CR and metoprolol OROS provided fairly constant drug release rates from 2–3 hr and up to 12–16 hr (Fig. 1). This period was somewhat longer for the multiple-unit formulation since it contains the less soluble succinate salt (276 versus 472 mg/ml for the fumarate in water at 37°C). As shown previously, a lower drug solubility allows a greater fraction of the dose to be released at a constant rate (16). Also, and as a result of the different formulation principles applied in the two systems, their release properties during the first 2 hr were quite different with a more rapid initiation of the release process for the CR formulation.

Previous reports have suggested that drug release from both the CR and the OROS formulations is principally unaffected by changes in the dissolution test conditions (8,9). Overall, this was confirmed by the present study (Table I). However, the OROS tablet showed a slightly faster drug release in simulated gastric juice, which resulted in a somewhat wider range for the mean dissolution time values (7.10–8.56 hr) compared to the CR formulation (8.19–8.97 hr), considering the pH interval 1.2–6.8 and the agitation rates 50 and 100 rpm.

Steady-State Pharmacokinetics

Overall, the ANOVA analyses resulted in several significant differences for the factors treatment and subject, but there was no evidence of effects related to the treatment periods.

Analysis of the predose (24-hr) plasma concentrations on days 5–8 indicated that steady state was attained on day 5 for metoprolol CR and the conventional metoprolol tablet and on day 6 for metoprolol OROS. Thus, estimation of C_{min} and related variables were based on the predose values from days 6, 7, and 8.

The mean plasma concentrations on days 5 (predose values) to 8 including full-time profiles for the concentration over two dosing intervals are depicted in Fig. 2 for the three metoprolol treatments. A summary of the pharmacokinetic variables and the 90% confidence intervals for the comparison between CR and OROS is given in Table II.

All three treatments provided reproducible and consistent plasma concentrations from day to day at steady state, although with large (about 10-fold) intersubject variation. In accordance with previously reported results (3,5), once-daily dosing with the CR or OROS delivery systems provided considerably lower peak plasma concentrations, longer times to achieve C_{max}, and three- to fourfold higher trough concentrations compared with the immediate-release tablet (Table II). Consequently, fluctuations in plasma levels over the dosing interval were considerably less pronounced (six to eight

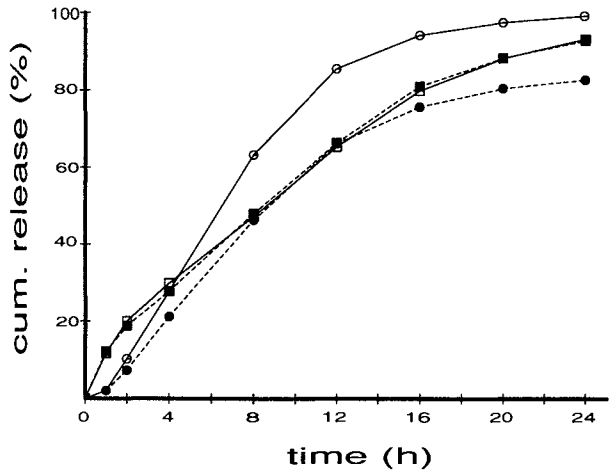

Fig. 1. Cumulative *in vitro* dissolution profiles for metoprolol CR (95 mg metoprolol succinate; squares) and metoprolol OROS (95 mg metoprolol fumarate; circles). Mean of six tablets, determined at a paddle speed of 50 rpm in simulated gastric juice, pH 1.2 (open symbols), and in a phosphate buffer solution, pH 6.8 (filled symbols).

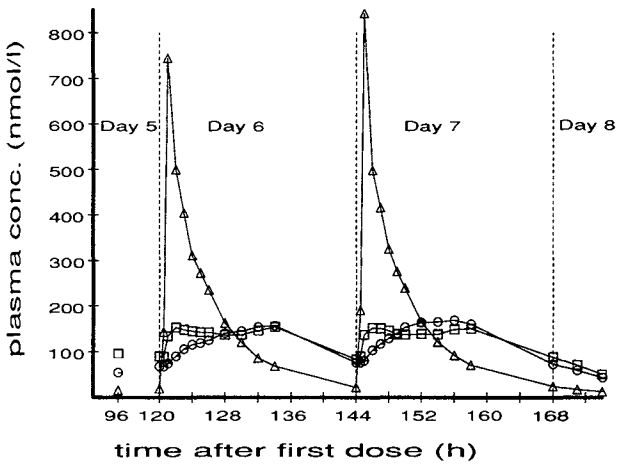

Fig. 2. Mean plasma concentrations of metoprolol on treatment days 5 (predose) through 8 following once-daily dosing of (□) metoprolol CR (95 mg metoprolol succinate), (○) metoprolol OROS (95 mg metoprolol fumarate), and (△) conventional metoprolol tablets (100 mg metoprolol tartrate) in 18 healthy subjects.

Table II. Mean (SD) Pharmacokinetic Variables for 18 Subjects on Days 6 and 7 Following Once-Daily Treatment with Metoprolol CR, OROS, and CT[a]

Variable	Treatment and day										Comparison CR vs OROS, 90% CI
	CR				OROS				CT		
	Day 6		Day 7		Day 6		Day 7		Day 6		Day 7		
C_{max} (nM)	171	(137)	166	(132)	172	(146)	187	(152)	721	(307)	852	(423)	81–111%
t_{max} (hr)[b]	6.7	(5.1)	7.1	(5.7)	9.7	(3.8)	10.0	(2.7)	1.2	(0.4)	1.1	(0.2)	−4.5 to −1.0 hr
C_{min} (nM)[c]	87 (94)				72 (84)				23 (40)				93–147%
AUC (nmol · hr/L)	3176	(2862)	3152	(2873)	2915	(2726)	3161	(2838)	3660	(3078)	3844	(3224)	92–115%
Fluctuation (%)	80	(26)	78	(30)	97	(29)	103	(28)	578	(201)	649	(217)	69–87%
MRT (hr)	14.0	(2.6)	14.4	(3.0)	14.2	(2.9)	13.8	(2.7)	5.7	(2.5)	5.7	(2.7)	94–109%

[a] Statistical comparisons between CR and OROS were based on the mean values from days 6 and 7 and are provided as 90% confidence intervals (CI).
[b] Statistical analysis of t_{max} was performed nonparametrically.
[c] Calculation of C_{min} was based on the predose steady-state concentrations on days 6, 7, and 8.

times) for the two extended-release formulations. Further, as a result of absorption being the rate-limiting process for CR and OROS, their mean residence times in the body were 8–9 hr longer than following administration of the immediate release tablet. This is also in accordance with the mean time for *in vitro* dissolution of the two products (Table I).

Based on comparison of AUC data, the mean (SD) relative bioavailability of metoprolol CR in relation to CT was 0.84 (0.22) and 0.79 (0.17) on days 6 and 7, respectively. The corresponding values for metoprolol OROS were 0.78 (0.27) and 0.83 (0.29). The reduced bioavailability for CR and OROS is probably a combination of effects: the slow drug input rate, which allows maximal hepatic extraction of metoprolol before entering the systemic circulation (17), and incomplete drug delivery and absorption. The contribution of the latter is indicated in Table III, which shows the metoprolol fumarate content in the OROS tablets which were collected after gastrointestinal (GI) passage in some individuals. In most cases almost all active drug had been released from the tablet prior to expulsion, but there were some instances of the reverse. In one extreme case over 50% of the dose still remained in the tablet.

The two once-daily metoprolol products were bioequivalent in C_{max} and AUC, with 90% confidence intervals for the mean ratio CR/OROS of 81–111 and 92–115%, respectively (Table II). However, their slightly different plasma concentration–time profiles resulted in a significantly lower fluctuation in plasma levels and a few hours earlier t_{max} for the CR formulation. For C_{min}, the confidence intervals were too wide to make any definite conclusion regarding bioequivalency between the two products.

Urinary Excretion Data

Elimination of metoprolol and the two oxidative metabolites in the urine were consistent for each treatment between the two dosing intervals (Table IV). Although there were no pronounced differences between the treatments, the recovered amounts were slightly lower for the two extended-release formulations compared to the immediate-release tablet. On day 6 the mean total amount recovered of the three compounds represented 71% (CR), 68% (OROS), and 78% (CT) of the given metoprolol dose (292 μmol). The corresponding values on day 7 were 76% (CR), 73% (OROS), and 80% (CR), respectively. Unless there is any unexpected difference between treatments with respect to other urinary metabolites (e.g., H 104/83), the approximately 10% lower relative recovery obtained for the two extended-release formulations is probably due to incomplete drug absorption.

Because of the polymorphic nature of metoprolol metabolism, the α-hydroxylation of the drug is greatly impaired in poor metabolizers (5–10% of Caucasians) (18). Thus, in a large unselected population the ratio of metoprolol to the 4-OH metabolite in urine can be expected to show a bimodal distribution (19). In this study subjects were characterized with respect to their oxidation phenotype by plotting indi-

Table III. Metoprolol Fumarate Content (mg/Tablet) in OROS Tablets Collected from Feces in Nine Subjects

	Subject no.											
	4	6	10	10	11	12	13	13	15	16	18	18
Study day	8	7	6	8	2–6[a]	4	6	7	5	5	5	7
Drug content (mg/tablet)	1.1	1.3	12.9	4.2	22.7	54.2	2.2	3.0	3.1	0.2	1.5	6.4

[a] For subject No. 11, a total of five tablets was collected on days 2–6. These were pooled and thus analyzed in one sample.

Table IV. Excretion of Metoprolol and Two Metabolites (H 117/04 and H 119/66) in Urine During Two Steady-State Dosing Intervals Following Once-Daily Administration of Metoprolol CR, OROS, and CT in 18 Healthy Subjects[a]

	Treatment and day					
	CR		OROS		CT	
Compound	Day 6	Day 7	Day 6	Day 7	Day 6	Day 7
Metoprolol	7.9 (6.9)	7.7 (6.5)	6.8 (6.4)	7.1 (6.2)	7.9 (7.8)	7.7 (7.7)
	1.3–26.0	2.1–25.7	1.4–24.7	1.3–24.0	1.4–29.4	1.6–31.2
H 117/04	53.7 (8.4)	57.4 (10.8)	51.6 (12.4)	56.0 (8.7)	59.5 (6.7)	62.1 (4.7)
	38.7–68.5	37.7–86.0	25.7–68.8	39.4–70.9	42.1–67.8	46.9–69.2
H 119/66	9.8 (3.8)	10.5 (4.8)	9.1 (3.9)	10.0 (4.0)	10.3 (4.1)	10.8 (4.2)
	0–13.7	0–20.5	0–13.9	0–15.9	0–16.0	0–14.7
Meto:H 119/66	0.98 (1.36)	0.95 (1.30)	0.86 (1.15)	0.81 (1.01)	0.94 (1.34)	0.86 (1.31)
ratio (n = 17)[b]	0.13–5.33	0.15–5.00	0.10–4.51	0.10–3.84	0.09–4.80	0.11–5.26

[a] Mean (SD) and range values expressed as a percentage of the given metoprolol dose (292 μmol). Also given is the urinary excretion ratio, metoprolol/4-OH metoprolol (H 119/66).

[b] One subject (No. 7) did not form any 4-OH metoprolol and thus could not be included in the calculation of the mean urinary excretion ratio. The ratio for this subject was set to >10 as shown in Fig. 3.

vidual values for the estimated elimination half-life of metoprolol following administration of the conventional tablet on days 6 and 7 (mean value) versus the urinary excretion ratio; metoprolol/4-OH metoprolol (log scale). This plot (Fig. 3) suggested three separate groups of individuals with respect to their capacity to metabolize metoprolol. Fourteen of the subjects included in this study were extensive metabolizers with a ratio (meto/4-OH meto) of less than 1 and a plasma elimination half-life between 2 and 4 hr. Three subjects probably had an intermediate metabolic capacity as indicated by their somewhat longer half-life (5–6 hr) and higher excretion ratio. Finally, one poor metabolizer was identified who had a plasma half-life of 9.3 hr and did not produce the 4-OH metabolite at all following any metoprolol administration. Since the four latter subjects also produced the largest plasma AUC's of metoprolol on both days in all three treatment periods, it can be assumed that the intrinsic metabolic capacity of an individual is not affected by a changed drug input rate.

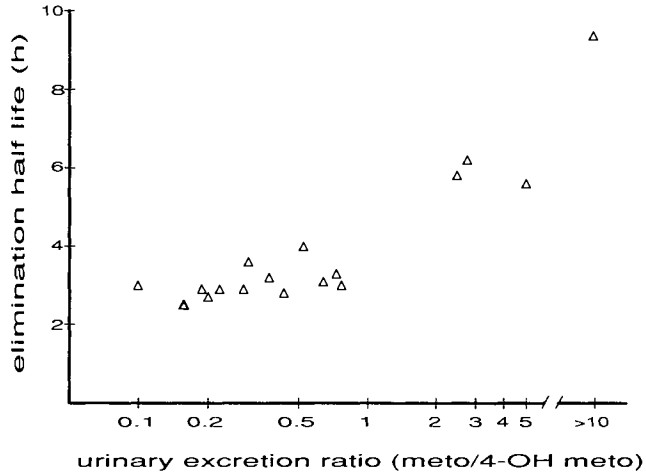

Fig. 3. Relationship between the plasma elimination half-life of metoprolol and the urinary excretion ratio of metoprolol/4-OH metoprolol (log scale) for each individual. The symbols represent the mean values determined on days 6 and 7 following administration of the conventional metoprolol tablet, 100 mg.

Day-to-Day Variability

The percentage day-to-day variation in AUC is shown in Fig. 4 for each individual and treatment. The median (extreme) values were 5.5 (13.8), 13.8 (52.2), and 9.4% (35.1%) for CR, OROS, and CT, respectively. The differences were not significant between either of the extended-release products and the conventional tablet. However, when comparing the multiple-unit CR formulation with the single-unit OROS tablet, the former system provided significantly lower (P = 0.017) variation in AUC between the two treatment days at steady state. Identifying the subjects for each treatment did not reveal any systematic pattern in the day-to-day variation of AUC (Fig. 4).

CONCLUSION

Metoprolol CR and metoprolol OROS both deliver most of their metoprolol dose at a slow and relatively constant rate in order to provide continuous drug absorption over a once daily dosing interval. The minor dissimilarities revealed regarding their *in vitro* dissolution properties can be ascribed to the different metoprolol salts and formulation principles used in the two systems.

Unlike immediate-release tablets, once-daily administration of the CR and OROS formulations results in consistent steady-state plasma concentrations with small peak-trough fluctuations over the dosing interval. Their relative bioavailability is reduced by about 20% compared to the conventional tablet, an effect which can be attributed to increased first-pass metabolism and to incomplete drug delivery.

The two extended-release products were bioequivalent for C_{max} and AUC based on the 90% confidence intervals for the mean ratio CR/OROS and the currently accepted criteria for equivalence. The day-to-day variability of AUC was significantly lower for the multiple-unit CR formulation, indi-

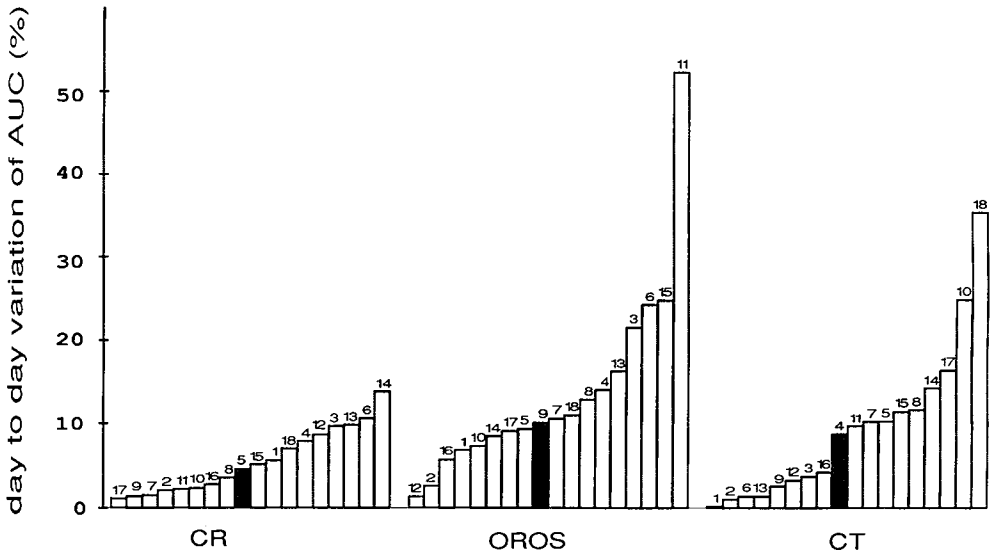

Fig. 4. Percentage day-to-day variation of AUC for each subject and treatment. Values were determined from the absolute AUC difference (day 6–day 7) divided by the mean AUC for the 2 days. Each bar represents one individual, identified by subject number and depicted in ascending order of day-to-day variation. The shaded bars indicate variation for the middle (ninth) subject.

cating the existence of formulation-related differences in the *in vivo* behavior of these two products, despite being considered bioequivalent. These dissimilarities are probably related to intraindividual differences in the gastrointestinal transit and absorption of the multiple-unit system versus the single-unit tablet, the former apparently being less variable in the present case. Although hardly of clinical importance for a drug like metoprolol, there may be *in vivo* differences between two dosage forms that have been found to be bioequivalent. It is therefore reasonable to include a study design with replicate steady-state plasma concentration measurements as a routine in new dosage form development, particularly in the testing program of novel drug delivery systems.

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