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 Cmax 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 β1-selective adrenoreceptor antagonist with wide therapeutic usage, particularly in the management of hypertension and ischemic 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 β1 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 β1 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 β1 blockade after once-daily dosing over a wide dosage range (2–5). They also appear to be more β1 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 pre-study 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-
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 speci-
fied 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

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

Metropolol OROS (OROS), Ciba-Geigy, lot No. L 001,
contains 95 mg of metropolol 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 metropolol tar-
tate. These quantities of the three salts are dose equivalent
with respect to the metropolol base. All study medications
were commercial compositions.

Sampling and Analysis

Five-milliliter venous blood samples for analysis of
metropolol 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. Metropolol plasma concen-
trations were measured by gas chromatography with elec-
tron-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 nM
(SD rel ≤ 15%).

A blank urine sample was collected on day 1 prior to
drug administration. After emptying the bladder before dos-
ing 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 metropolol 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) metropolol (12). The three compounds
were determined by column liquid chromatography and flu-
orometric detection (13). The minimum determinable concen-
tration of the assay was 1 μM (metropolol), 2 μM (H 117/04),
and 1 μM (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 remain-
ing drug (metropolol 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 deter-
mination of metropolol at 274 nm. Statistical moment analy-
ysis was used to determine the mean time for in vitro disso-
lution of these profiles (14).

Calculations and Statistics

Attainment of steady state was examined in each treat-
ment 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 differ-
ence.

The pharmacokinetic variables estimated for each sub-
ject and treatment on days 6 and 7 were Cmax, tmax, 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:

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

where \(\tau = 24 \text{ hr}\). Cmin was defined as the mean of the pre-
dose (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, Cmax, MRT, and per-
centage 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 Metropolol Succinate and Metropolol Fumarate from CR and OROS, Respectively* |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | 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            |

* 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.