PHARMACOKINETIC AND PHARMACODYNAMIC COMPARISON OF CONVENTIONAL AND CONTROLLED RELEASE FORMULATIONS OF METOPROLOL IN HEALTHY CHINESE SUBJECTS

SUMMARY. A double-blind, crossover comparison of the pharmacokinetics and pharmacodynamics of controlled-release metoprolol (CR) 100 mg and 200 mg, metoprolol plain tablet 100 mg, metoprolol Durules 200 mg, and placebo was carried out in 10 healthy Chinese subjects. Standardized treadmill exercise tests according to the Bruce protocol were performed at a steady state of medication, before and 2, 6, 12, and 24 hours after the dose, and multiple blood samples were collected for determination of the metoprolol concentration. The plasma metoprolol levels over 24 hours were more uniform after metoprolol CR than Durules and the plain tablet. The mean peak concentrations for CR 100 mg, 200 mg, Durules, and the plain tablets were 231, 426, 790, and 1105 nmol/l, respectively. The corresponding fluctuation incides were 1.1, 1.5, 2.2, and 5.0. The effects on exercise heart rate (EHR) were investigated at steady state. Metoprolol CR produced more even reduction in EHR over 24 hours than Durules and plain tablets. All four treatments gave similar maximal reduction in EHR of about 20% at 2 hours after the dose. In conclusion, once-daily metoprolol CR showed almost even blood levels and provided relatively constant levels of beta-blockade over 24 hours in healthy Chinese subjects.

KEY WORDS. metoprolol, controlled-release formulation, conventional tablet, plasma concentration, exercise heart rate

Metoprolol, a cardioselective beta-adrenoceptor antagonist without intrinsic sympathomimetic activity, has become widely used in the management of hypertension and ischemic heart disease. In recent years, it has been suggested that metoprolol may also play a cardioprotective role by improving long-term survival [1] and quality of life [2] after myocardial infarction. Recently, the MAPHY study [3] showed that starting antihypertensive treatment in men with mild to moderate hypertension with metoprolol instead of a thiazide diuretic reduced total and cardiovascular mortality. It would seem, therefore, that the maintenance of adequate and even levels of beta-blockade throughout 24 hours for continuous cardioprotection may be of clinical importance.

A new controlled-release (CR) dosage form of metoprolol, based upon the microcoating principle, has recently been developed [4]. The active ingredient, metoprolol succinate, is divided into several small dose units, which release metoprolol during the entire passage through the gastrointestinal canal. Previous studies [5–7] in healthy Caucasian subjects have shown that once-daily dosing with this formulation produced an even plasma concentration-time profile over 24 hours. Furthermore, the peak plasma concentration is considerably reduced, which may imply potentially better tolerance, especially with respect to fatigue and bradycardia.

Pharmacologic studies with metoprolol in Asian subjects are lacking and a comparison of metoprolol in different formulations in Chinese has never been performed. In the present study the steady-state pharmacokinetic and pharmacodynamic properties of metoprolol CR 100 mg and 200 mg, metoprolol plain tablet 100 mg, and metoprolol Durules 200 mg were compared in healthy Chinese volunteers.

Subjects and Methods

Subjects

Ten healthy Chinese males, aged (mean ± SEM) 28.8 ± 1.5 years (range 23–37 years), weight 60.6 ± 1.4 kg (range 57–67 kg) were included in the study. All were

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judged healthy as determined by medical background, physical examination, laboratory investigation, and electrocardiogram. No subjects took any prescribed medicines in the 2 weeks before the start of the study. The purpose of the study was explained to each subject, all of whom freely consented to participate.

Study Design

The study was a double-blind, five-way, crossover comparison of metoprolol CR 100 mg and 200 mg, metoprolol plain tablets 100 mg, metoprolol Durules 200 mg (all products of Astra, Sweden), and placebo, dosed to steady state. The drugs were given in a randomized order. Each treatment period consisted of 4 days, with a washout period between treatments of at least 3 days.

The subjects visited the laboratory on 2 consecutive days in each treatment period. On study days 1–3, the subjects took the drugs at home. Subjects were instructed to take the tablets with water in the morning at least half an hour before breakfast. They were further instructed not to change their breakfast habits from one day to another during the study period. On day 4, the subjects came to the laboratory about 08.00 hours, having abstained from food, fluids, and tobacco since 22.00 hours the previous evening. A plastic catheter was inserted into a cubital vein for blood sampling to determine metoprolol plasma levels. After performance of the first exercise test, the study drug was administered, and further exercise tests and blood samplings were performed according to a standardized schedule over the next 12 hours. Standardized meals were served during the day. The subjects returned to the laboratory in the next morning (i.e., 24 hours after dose) for a final exercise test and blood sampling.

The subjects were instructed to avoid strenuous exercise during the treatment periods. No alcohol or over-the-counter drugs were permitted from 2 days before each study period until the blood sampling was completed. Laboratory screens were performed before the first test dose and on day 4 of each treatment period.

The study was conducted under conditions that were in compliance with the Declaration of Helsinki.

Exercise Tests and Blood Sampling

Standardized exercise tests were performed on a treadmill according to the Bruce protocol [8]. Prior to the definitive study, subjects were familiarized with the exercise testing procedure, and the stage at which a steady heart rate of about 150 beats/min was achieved was individually titrated. This was defined as submaximal exercise. In the preliminary run, all subjects achieved the required heart rate during stage III exercise. In the double-blind study, each exercise test was performed according to the same procedure. The heart rate and systolic blood pressure achieved during the last minute of stage II exercise were measured.

Five milliliter venous blood samples were collected for analysis of metoprolol concentrations on day 4 at the following times: 10 minutes before and 1, 2, 3, 4, 6, 8, 12, and 24 hours after administration of the study drugs. The plasma was separated and samples were kept frozen until analysis. The metoprolol plasma concentrations were determined by high-resolution gas chromatography with electrol capture detection [9] in the Department of Analytical Chemistry (AB Hassle, Sweden). The minimum detectable concentration was 10 nmol/l (SD<sub>rew</sub> 10%).

Calculations and Statistics

The plasma concentration-time profiles were described by the following pharmacokinetic parameters: C<sub>max</sub>, C<sub>min</sub> (maximum and minimum concentrations), t<sub>max</sub> (time to reach peak concentration), AUC (area under the plasma concentration-time curve, 0 to 24 hours) and a fluctuation index (FI) calculated to express the peak-trough fluctuation of plasma concentrations. The fluctuation index was calculated using the following equation [10]:

\[ \text{FI} = \frac{C_{\text{max}} - C_{\text{min}}}{\text{AUC}/T} \]

where T = the dosage interval.

The elimination half-life (T<sub>1/2</sub>) of metoprolol was determined from the terminal slope of the semi-logarithmic plot of the plasma level-time curve of the plain tablet.

The pharmacodynamic effect of the drug was expressed as the percentage reduction in EHR in relation to placebo. The difference between the maximum effect (E<sub>max</sub>) and minimum effect (E<sub>min</sub>) was calculated to indicate the fluctuation in the beta-blocking effect.

For all pharmacodynamic and pharmacokinetic variables, the significance of differences observed was established by means of Student's paired t test. Adjustments were made for multiple comparisons. For all tests of significance, a p value less than or equal to 0.05 was considered as statistically significant.