Pharmacokinetic Variability of Routinely Administered Bisoprolol in Middle-Aged and Elderly Japanese Patients

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The nonlinear mixed effects model (NONMEM) was used to analyze the pharmacokinetics of routinely administered bisoprolol in middle-aged and elderly Japanese patients. The subjects consisted of 29 males and 11 females with a mean age of 63.5±10.1. Data on the plasma concentration of bisoprolol from 94 blood samples obtained at steady-state following repetitive oral administration were analyzed using the NONMEM program, where a one-compartment model with repetitive bolus dosing was parameterized in terms of oral clearance (CL/F) and apparent volume of distribution (V/F). Individual CL/F values were correlated with body weight (WT) and creatinine clearance (CLcr). The relation between CLcr and the CL/F of bisoprolol was not altered by the CYP2D6 and CYP2C19 genotypes, gender, or age. The mean CL/F value estimated with NONMEM was 0.0612·WT+1.15·CLcr (l/h), and the mean V/F value was 2.61·WT (l). The residual interindividual variability of CL/F and V/F were 22.0% and 12.6%, respectively. The pharmacokinetic variability of bisoprolol is small even in routinely treated Japanese patients, provided that both body weight and renal function are taken into account for the prediction of oral clearance of the drug.

Key words Japanese; elderly patient; bisoprolol; pharmacokinetics; nonlinear mixed effects model (NONMEM)

Pharmacokinetic variability of bisoprolol is an important parameter for understanding the drug's behavior in the body. Bisoprolol is a selective β1-blocker with intrinsic sympathomimetic activity, and it has been widely used in patients with cardiovascular diseases such as hypertension, angina pectoris, and cardiac arrhythmias in Japan. In healthy young subjects, 50% of the total dose of bisoprolol is metabolized in the liver, while 50% is excreted via the kidneys unchanged. The pharmacokinetics of bisoprolol show less interindividual variability than that of other β-blockers because of a nearly complete absorption, small hepatic first-pass metabolism, and balanced renal excretion. In elderly patients, however, the age-associated decline in glomerular filtration rate can affect the elimination of a drug dependent on the kidney for excretion. In addition, hepatic drug metabolism may be diminished due to decreases in hepatic blood flow, liver mass, and levels of cytochrome P450 (CYP) drug-metabolizing enzymes. However, the pharmacokinetics of bisoprolol have not been clarified in routinely treated elderly Japanese patients.

The present study was designed to evaluate the pharmacokinetic variability of routinely administered bisoprolol in middle-aged and elderly Japanese patients. A pharmacokinetic analysis was performed using a nonlinear mixed effects model (NONMEM). In addition, it is reported that drug metabolism activity is often genetically polymorphic. In this study, therefore, we also evaluated the effects of well-known genetic polymorphisms of CYP2D6 and CYP2C19 on the pharmacokinetic variability of bisoprolol.

MATERIALS AND METHODS

Subjects and Study Protocols The subjects were 29 male and 11 female Japanese patients aged between 43 and 89 (mean±S.D.: 63.5±10.1) years old, and mean body weight (±S.D.) was 63.8±10.7 kg. In this study, seven patients were characterized as having New York Heart Association (NYHA) class II congestive heart failure (CHF), but no patients had severe cardiac, hepatic, or renal failure. That is, mean (±S.D.) values of serum creatinine concentration, glumatic oxaloacetic transaminase activity, and glumatic pyruvic transaminase activity in the patients were 0.82±0.19 mg/dl (range: 0.50—1.30 mg/dl), 26±11 IU/l (range: 9—65 IU/l), and 29±26 IU/l (range: 4—160 IU/l), respectively. All patients had been routinely treated with an oral administration of bisoprolol hemifumarate (Maintate® Tablets, Tanabe Pharmaceutical Co., Osaka, Japan) at doses of 2.5 or 5 mg/d, and the drug was administered once a day in all patients. No patients had received any potent inhibitor of CYP2D6 (e.g. amiodarone and quinidine) concomitantly. The total number of blood samples obtained at steady-state following repetitive administration was 94. That is, one or two blood samples for all 40 patients were obtained between 2.3 and 7.0 h after the administration. Additional blood samples just before administration were obtained in 36 patients. All patients (11 inpatients and 29 outpatients) gave written consent to participate in this study, which was approved by the ethics committee of Toyama Medical and Pharmaceutical University.

Assay of Bisoprolol Plasma concentrations of bisoprolol were determined by a reversed-phase HPLC method. A 0.5 ml aliquot of plasma was alkalized with 3 ml of glycine buffer (0.1 M, saturated with NaCl, pH 10.6), and mildly extracted with 5 ml of diethylether for 20 min. Bisoprolol was back-extracted from the organic phase with 0.2 ml of 0.05 N HCl. A 50 µl aliquot of HCl solution was injected onto an HPLC system. The column was COSMOSIL 5C18-AR-II (15 cm×4.6 mm; i.d. 4.5 µm particle size; Nacalai tesque). The mobile phase consisted of 10 mM KH2PO4/acetonitrile (84/16) that contained 0.95% (w/v) triethylamine adjusted to pH 3.3 with phosphoric acid. The peaks were monitored at an excitation wavelength of 228 nm and an emission wavelength of 298 nm. The coefficient of variation of this assay was 3.3% and 4.4% at a plasma bisoprolol concentration of 5 ng/ml and 20 ng/ml, respectively. The detection limit for...
Pharmacokinetics of Bisoprolol

The time required to reach the peak concentration after oral administration of bisoprolol (Maintate® Tablets) is determined by the polymerase chain-reaction fragment length polymorphism (PCR-RFLP) method and CYP2D6 was detected by the allele-specific PCR method. In addition, the detection of CYP2D6*5 was carried out using two kinds of long-PCR. Reduction in metabolic activity of CYP2D6. The 40 patients were classified into three groups on the basis of the number of these alleles. That is, Group 1 consisted of the patients without CYP2D6*5, *10, and *14 allele. Group 2 consisted of the heterozygotes of CYP2D6*5, *10, or *14 allele. Group 3 consisted of the homozygotes of CYP2D6*5, *10, or *14 alleles. The CYP2C19*1 (wild-type) allele and two defective allelic variants, CYP2C19*2 and CYP2C19*3, were also determined by the PCR-RFLP method. The subjects homozygous for CYP2C19*1 and heterozygous for the mutant alleles (CYP2C19*1/*2 and *1/*3) were defined as extensive metabolizers of CYP2C19-related drugs. Those homozygous for the mutant alleles (CYP2C19*2/*2, *2/*3, and *3/*3) were defined as poor metabolizers of CYP2C19.

Nonlinear Mixed Effects Model for Analyzing the Pharmacokinetics of Bisoprolol

The time required to reach the peak concentration after oral administration of a conventional preparation of bisoprolol (Maintate® Tablets) is short (mean±S.D.: 3.0±1.0 h). In the present study, no plasma concentration data of bisoprolol was obtained at the absorption phase (0—2.3 h after oral administration). Therefore, the one-compartment model with repetitive bolus dosing was parameterized in terms of CL/F and V/F. For the simplest basic model (Model 1), the oral clearance in the ith individual (CL/F) was modeled using the following equation:

\[
CL/F = \theta_1 \cdot WT \cdot (1 + \eta_{CL/F})
\]

where \(\theta_1\) is the predicted population mean of oral clearance, \(WT\) is the individual body weight, and \(\eta_{CL/F}\) is a random variable distributed with a mean of zero and variance of \(\omega_{CL/F}^2\). The apparent volume of distribution in the ith individual (V/F) was modeled using the following equation:

\[
V/F = \theta_2 \cdot WT \cdot (1 + \eta_{V/F})
\]

where \(\theta_2\) is the predicted population mean of the apparent distribution volume, and \(\eta_{V/F}\) is a random variable with a mean of zero and variance of \(\omega_{V/F}^2\). Finally, the jth observed plasma concentration in the ith patient (\(C_p_{ij}\)) was assumed to be randomly and normally distributed from the jth predicted plasma concentration in the ith patient (\(C_p_{ij}^\beta\)):

\[
C_p_{ij} = C_p_{ij}^\beta + \epsilon_{ij}
\]

where \(\epsilon_{ij}\) is a random variable that describes intraindividual variability with a mean of zero and variance of \(\sigma^2\).

Table 1 summarizes the 14 analysis models used in this study. In Model 2, we modeled CL/F as the sum of non-renal clearance and renal clearance, where the first term (\(\theta_3 \cdot WT\)) and the second term (\(\theta_4 \cdot CLcr\)) of the equation represent non-renal and renal clearance, respectively. The CLcr value (in l/h) was calculated using the Cockcroft-Gault equation as follows:

\[
CLcr = \frac{(140 - AGE) \cdot WT}{72 \cdot Scr} - 0.85 \cdot \frac{6.0}{1000}
\]

where \(AGE\) is age, \(WT\) is body weight, \(Scr\) is serum creatinine concentration (in mg/dl), and \(SEX\) is one for females and zero for males. The effects of body weight on CL/F and V/F were evaluated with Models 3 and 4, respectively. The effects of age on CL/F and V/F were evaluated using Models 5, 6, 7, and 8; where \(AGE \leq 65\) is one for the older (65—89 years old) patients, and zero for the younger (43—64 years old) patients. Models 9 and 10 were used to evaluate the effects of gender on CL/F and V/F, respectively. In addition, the effects of CYP2D6*10 on CL/F were evaluated with Models 11 and 12; where \(G1 = 1\) and \(G2 = 0\) for Group 1 patients with CYP2D6*1/*1, *1/*2, and *2/*2; \(G1 = 0\) and \(G3 = 0\) for Group 2 patients with CYP2D6*1/*10, *2/*10, and *2/*3; and \(G1 = 0\) and \(G3 = 1\) for Group 3 patients with CYP2D6*10/*10. The effect of CYP2D6*2 on CL/F was evaluated with Model 13; where 2D6*2 is one for patients with at least one CYP2D6*2 allele and zero for patients without CYP2D6*2. Model 14 was used to evaluate the effect of the CYP2C19 defect on CL/F; where 2C19PM is one for poor metabolizers of CYP2C19 and zero for extensive metabolizers.

Data Analysis

Data analysis was performed with NONMEM software (double precision NONMEM Version V Level 1.1, PREDPP Version IV Level 1.1, and NM-TRAN Version III Level 1.1) running on a mainframe UNIX computer at the Kyoto University Data Processing Center. In the present study, we used a first-order estimation method and the NONMEM-PREDPP library subroutines ADVAN1 and TRANS2 for the one-compartment model with bolus dosing. The statistical significance of the parameters was evaluated with the likelihood ratio test using the minimum value of the objective function (−2 log likelihood) produced by NONMEM. The difference of −2 log likelihood (LLD) is asymptotically distributed as \(\chi^2\) with degrees of freedom equal to the number of parameters that were fixed to hypothesis value. That is, when the LLD value between two models allowing a parameter of interest freely estimated versus a fixed hypothetical value was greater than 3.84, the parameter value was considered to be statistically significant (\(p<0.05\)). In addition, NONMEM provides estimates of the standard error (S.E.) for all parameters, and S.E. can be used to define 95% confidence intervals (CI) for true parameter values: 95% CI=(the estimated parameter value)±1.96·S.E.

Statistical Analysis

Values are expressed as mean±S.D. Statistical significance of difference between mean values was calculated using a non-paired t-test. Multiple comparison was performed using Scheffe’s test following one-way ANOVA. \(p\) values of less than 0.05 were considered to be significantly different.
RESULTS

Figure 1 shows the mean plasma concentration of bisoprolol in individual patients. The 40 patients were classified into three groups on the basis of the CYP2D6 genotype, which is shown in Table 2. Fourteen patients were classified into Group 1: eight patients were homozygous for the CYP2D6*1 allele, five were heterozygous for the CYP2D6*1/*2 alleles, and one was homozygous for the CYP2D6*2 allele. Seventeen patients were classified into Group 2: fourteen patients were heterozygous for the CYP2D6*1/*10 alleles, two were heterozygous for the CYP2D6*2/*10 alleles and one was homozygous for the CYP2D6*2/*10 alleles. Nine patients homozygous for the CYP2D6*10 allele were classified into Group 3. Mean plasma concentrations of bisoprolol at 2.3—7.0 h after the dose in Group 1, Group 2, and Group 3 were 21.6±6.4 ng/ml, 23.1±10.3 ng/ml, and 23.1±10.4 ng/ml, respectively. Mean plasma concentrations of bisoprolol just before administration in Group 1, Group 2, and Group 3 were 6.6±2.7 ng/ml, 7.5±3.8 ng/ml, and 6.1±3.9 ng/ml, respectively. No significant effect of genetic polymorphisms of CYP2D6 was observed on the plasma levels of bisoprolol in Japanese patients (Fig. 1).

Table 1 summarizes 14 analysis models for the pharmacokinetic parameters and the LLD values obtained in this study. The population mean pharmacokinetic parameters, $\theta_1$ and $\theta_3$, for Model 1 were estimated to be 0.149 l/h/kg and 2.62 l/kg, respectively. The $\omega_{CL/F}$ and $\omega_{V/F}$ values for Model 1 were estimated to be 29.5% and 15.0%, respectively. The LLD value for Model 2 was 12.53 (Table 1), indicating a significant effect of renal function on the pharmacokinetic variability of bisoprolol ($p<0.001$). Therefore, the $CL/F$ of bisoprolol was described as the sum of non-renal and renal clearance in the subsequent analysis.

The $\theta_4$ and $\theta_5$ values were estimated to be 0.821 and 0.766, respectively; however, the LLD values were only 0.16 and 1.04 for Models 3 and 4, respectively (Table 1). The $\theta_6$ value for Model 5 and the $\theta_7$ value for Model 6 were estimated to be 1.16×10$^{-3}$ l/h/kg and 0.795, respectively. The $\theta_8$ value for Model 7 and the $\theta_9$ value for Model 8 were estimated to be 1.23×10$^{-10}$ l/kg and 0.992, respectively. The $\theta_{10}$

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**Table 1. Analysis Models for the Pharmacokinetic Parameters of Bisoprolol**

<table>
<thead>
<tr>
<th>Model</th>
<th>Formula</th>
<th>No. of $\theta$s</th>
<th>LLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$CL/F = \theta_1 \cdot WT \cdot (1 + \eta_{CL/F})$</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>$CL/F = (\theta_1 \cdot WT + \theta_2 \cdot CLcr) \cdot (1 + \eta_{CL/F})$</td>
<td>3</td>
<td>12.53 vs. Model 1</td>
</tr>
<tr>
<td>3</td>
<td>$CL/F = (\theta_1 \cdot WT \cdot q + \theta_3 \cdot CLcr) \cdot (1 + \eta_{CL/F})$</td>
<td>4</td>
<td>0.16 vs. Model 2</td>
</tr>
<tr>
<td>4</td>
<td>$CL/F = (\theta_1 \cdot WT + \theta_2 \cdot CLcr) \cdot (1 + \eta_{CL/F})$</td>
<td>4</td>
<td>1.04 vs. Model 2</td>
</tr>
<tr>
<td>5</td>
<td>$CL/F = (\theta_1 \cdot WT + \theta_2 \cdot CLcr) \cdot (1 + \eta_{CL/F})$</td>
<td>4</td>
<td>2.60 vs. Model 2</td>
</tr>
<tr>
<td>6</td>
<td>$CL/F = (\theta_1 \cdot WT + \theta_2 \cdot CLcr) \cdot (1 + \eta_{CL/F})$</td>
<td>4</td>
<td>1.96 vs. Model 2</td>
</tr>
<tr>
<td>7</td>
<td>$CL/F = (\theta_1 \cdot WT + \theta_2 \cdot CLcr) \cdot (1 + \eta_{CL/F})$</td>
<td>4</td>
<td>0.00 vs. Model 2</td>
</tr>
<tr>
<td>8</td>
<td>$CL/F = (\theta_1 \cdot WT + \theta_2 \cdot CLcr) \cdot (1 + \eta_{CL/F})$</td>
<td>4</td>
<td>0.01 vs. Model 2</td>
</tr>
<tr>
<td>9</td>
<td>$CL/F = (\theta_1 \cdot WT + \theta_2 \cdot CLcr) \cdot (1 + \eta_{CL/F})$</td>
<td>4</td>
<td>0.28 vs. Model 2</td>
</tr>
<tr>
<td>10</td>
<td>$CL/F = (\theta_1 \cdot WT + \theta_2 \cdot CLcr) \cdot (1 + \eta_{CL/F})$</td>
<td>4</td>
<td>0.61 vs. Model 2</td>
</tr>
<tr>
<td>11</td>
<td>$CL/F = (\theta_1 \cdot WT + \theta_2 \cdot CLcr) \cdot (1 + \eta_{CL/F})$</td>
<td>4</td>
<td>0.02 vs. Model 2</td>
</tr>
<tr>
<td>12</td>
<td>$CL/F = (\theta_1 \cdot WT + \theta_2 \cdot CLcr) \cdot (1 + \eta_{CL/F})$</td>
<td>4</td>
<td>0.04 vs. Model 2</td>
</tr>
<tr>
<td>13</td>
<td>$CL/F = (\theta_1 \cdot WT + \theta_2 \cdot CLcr) \cdot (1 + \eta_{CL/F})$</td>
<td>4</td>
<td>0.26 vs. Model 2</td>
</tr>
<tr>
<td>14</td>
<td>$CL/F = (\theta_1 \cdot WT + \theta_2 \cdot CLcr) \cdot (1 + \eta_{CL/F})$</td>
<td>4</td>
<td>0.12 vs. Model 2</td>
</tr>
</tbody>
</table>
value for Model 9 and the $\theta_{11}$ value for Model 10 were estimated to be 0.904 and 1.07, respectively. However, the LLD values in Model 5—10 did not reach a statistically significant level, indicating that age and gender had no significant effect on the non-renal clearance and $V/F$ of bisoprolol (Table 1). The $\theta_{12}$ value for Model 11 was estimated to be $9.56 \times 10^{-3}$ l/h/kg, but the LLD value in Model 11 was 0.02, confirming that the CYP2D6*10 allele had no significant effect on the non-renal clearance of bisoprolol (Table 1). In addition, no significant improvement by the introduction of $\theta_{13}$ was observed in the LLD value for Model 12. Similarly, the $\theta_{14}$ value for Model 13 was estimated to be 1.11, but the LLD value in Model 13 was 0.26, indicating that the CYP2D6*2 allele had no significant effect on the non-renal clearance of bisoprolol (Table 1). Seven of 40 patients were poor metabolizers of CYP2C19 (Table 2). The $\theta_{15}$ value for Model 14 was estimated to be 1.09; however, the CYP2C19 defect seemed to have no effect on the non-renal clearance of bisoprolol because of the small LLD value for Model 14 (Table 1). Consequently, Model 2 was selected as the final model to describe the pharmacokinetics of routinely administered bisoprolol in middle-aged and elderly Japanese patients.

Table 3 shows the final estimates of population pharmacokinetic parameters of bisoprolol and their 95% CI for Model 2. The mean values of $CL/F$ and $V/F$ were estimated to be 0.0612 $\cdot$ WT$+1.15$CLcr (l/h) and 2.61 l/kg, respectively. The final $\omega_{CL/F}$ and $\omega_{V/F}$ values for Model 2 were estimated to be 22.0% and 12.6%, respectively, which were less than those for Model 1. Figure 2 shows the effects of age and gender on the individual ($V/F$)/WT values of bisoprolol, where the pharmacokinetic parameters in individual patients were obtained from population estimates for Model 2 according to Bayes’ theorem using the NONMEM posthoc option. The mean age of female and male patients in the present study was 70.8±9.2 and 60.7±9.1 years, respectively. No significant effects of age and gender were observed on the ($V/F$)/WT values. Figure 3 shows the relationship between the CLcr/WT and ($CL/F$)/WT values of each patient. The CLcr/WT value in the younger (43—64 years old) and the older (65—89 years old) patients was 0.0887±0.0174/l/h/kg and 0.0685±0.0154/l/h/kg, respectively. The ($CL/F$)/WT value of bisoprolol was significantly ($p<0.05$) lower in the older patients (0.139±0.0361/l/h/kg) than younger patients (0.165±0.0291/l/h/kg). However, the relation between CLcr/WT and ($CL/F$)/WT in the older patients was not significantly different from that in the younger patients (Fig. 3).

DISCUSSION

The aim of this study was to evaluate the pharmacokinetic variability of routinely administered bisoprolol in Japanese patients. The present analysis shows that the individual $CL/F$ values of bisoprolol were correlated with the creatinine clearance (CLcr) value (Fig. 3). The relation between CLcr and CL/F of bisoprolol was not altered by the CYP2D6 and CYP2C19 genotypes, gender, or age (Fig. 3, Table 1). The mean $CL/F$ value estimated with NONMEM was 0.0612 $\cdot$ WT$+1.15$CLcr (l/h), and the residual interindividual variability of $CL/F$ was 22.0% (Table 3). The pharma-
kinetic variability of bisoprolol is small even in routinely treated patients, provided that both body weight and renal function are taken into account for the prediction of oral clearance of the drug.

Kirch et al. reported that the mean non-renal and renal clearance values of bisoprolol in healthy Caucasian subjects (mean age: 23 years old) were 0.0958 l/h/kg and 0.101 l/h/kg, respectively. 20 Horikiri et al. indicated that the mean non-renal and renal clearance values of bisoprolol in healthy Japanese subjects (mean age: 37 years old) were 0.058 l/h/kg and 0.108 l/h/kg, respectively. 21 In the present study, the mean non-renal clearance value of bisoprolol in middle-aged and elderly Japanese patients was estimated to be 0.061 l/h/kg which seemed to be compatible with that in the younger subjects (Table 3). On the other hand, our results suggested that renal function decreased with age, and that the reduced renal function resulted in the decrease of renal clearance of bisoprolol. That is, the mean calculated CLcr/WT value in the older (alsy65 years old) patients was 0.0685 l/h/kg, which was significantly smaller than that in the younger patients (<65 years old) patients (0.0887 l/h/kg, p<0.001, Fig. 3). Accordingly, the mean renal clearance values were estimated to be 0.0788 l/h/kg and 0.102 l/h/kg in the older (>65 years old) and younger (<65 years old) patients, respectively.

Horikiri et al. investigated the catalytic activity of the 10 different recombinant human CYP isoforms, including CYP2C19, CYP2D6, and CYP3A4, with respect to the O-deisopropylation of bisoprolol, and reported that only CYP2D6 and CYP3A4 show a substantial activity for the production of a major metabolite, O-deisopropyl-bisoprolol. 3 Moreover, they suggested that CYP2D6 has a minor role but CYP3A4 plays a major part in the metabolism of bisoprolol, because the content of CYP2D6 in the human liver is much lower than that of CYP3A4. 2,20 The present findings that the non-renal clearance was not altered by the CYP2D6 and CYP2C19 genotypes may be consistent with the report of Horikiri et al. 2,20 On the other hand, more than 30 single nucleotide polymorphisms have been identified in the CYP3A4 gene. 21 For the most common variant CYP3A4*1B, increased transcription was demonstrated in vitro, which may theoretically result in higher enzymatic activity in vivo. 22,23 However, the allele frequency ranges from 0% (Chinese and Japanese) to 45% (African-American). 21 In the present study, therefore, we could not investigate the effect of the polymorphism of CYP3A4 on the pharmacokinetics of bisoprolol in Japanese subjects.

We previously investigated the pharmacokinetics of metoprolol in middle-aged and elderly Japanese patients (mean age: 69.6±7.6 years old). 24,25 In a NONMEM analysis based on a one-compartment model, the population mean of the CL/F value and the CL/F value were estimated to be 0.811 l/h/kg and 69.7%, respectively. 25 The CL/F value in the patients homozygous for the CYP2D6*10 allele was 64% lower than that in the patients with a CYP2D6*1/*1 or *1/*2 genotype. 25 In addition, the CL/F value was 26% lower in the older (>70 years old) patients than younger (≤70 years old) patients. 25 Thus, when both CYP2D6*10 and age were taken into account for the pharmacokinetic analysis of metoprolol, the CL/F value was estimated to be 29.7%. 25 In the present study, the CL/F value of bisoprolol for the basic model (Model 1) was estimated to be 29.5% in middle-aged and elderly Japanese patients. Moreover, when renal function (CLcr) was taken into account for the pharmacokinetic analysis of bisoprolol (Model 2), the CLcr/F value was estimated to be 22.0% (Table 3). These results indicate that the pharmacokinetic variability of bisoprolol is smaller than that of metoprolol.

In this study, seven of 40 patients had CHF (NYHA class II), but no patients who had moderate to severe CHF (NYHA class III or IV) were included. A large clinical trial (CIBIS-II) in Caucasians has shown a beneficial effect of bisoprolol on patients with chronic heart failure (NYHA class III). 26 In addition, other clinical trials have suggested that metoprolol has a beneficial effect on CHF patients in NYHA class II to III, and that carvedilol has a similar effect on CHF patients in NYHA class II to IV. 27,28 In Japan, however, carvedilol is only one β-blocker demonstrated to have a beneficial effect on patients with CHF (NYHA class II to III), and the efficacy of bisoprolol and/or metoprolol has not been established in patients with CHF. 29 In order to establish the usefulness of bisoprolol and/or metoprolol in the treatment of Japanese patients with CHF, further studies evaluating the pharmacokinetic variability, as well as the clinical efficacy, of these drugs may be needed.

In conclusion, though the renal clearance of bisoprolol was significantly decreased in elderly patients, the pharmacokinetic variability of bisoprolol was relatively small even in routinely treated Japanese patients.

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