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Analysis of Clinical Efficacy and Adverse Effects of β-Blocking Agents Used Clinically for Chronic Heart Failure

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Clinical efficacy and adverse effects of the β-blocking agents, carvedilol, bisoprolol, and metoprolol were analyzed theoretically, and then compared quantitatively, for the purpose of determining their proper use for chronic heart failure. Initially, we evaluated occupancy binding to the β₁ and β₂ receptors (Φss₁ and Φss₂) by these drugs. Thereafter, we examined the relationship between Φss₁ values and left ventricular ejection fraction (LVEF) increase rate to determine efficacy. The result showed that the efficacy with carvedilol could be attained with a lower Φss₁ value than the others. Therefore, we constructed a model under the assumption that β-blocking agents exert both indirect action of LVEF increase through the β₁ receptor and direct action on ryanodine receptor 2. Using the model, it was suggested that these drugs have no differences in regard to the efficacy, while it was clarified theoretically that only carvedilol produces an effect that directly involves ryanodine receptor 2 at clinical doses. We also investigated decreases in heart rate and forced expiratory volume in 1 s as adverse effects of β-blocking agents using a ternary complex model. It was indicated that carvedilol is less likely to induce a heart rate decrease. Meanwhile, it was also suggested that the risk of an asthmatic attack was higher for carvedilol at clinical doses. Our results are considered useful for selection of a proper β-blocking agent and its administration at a reasonable dose for successful heart failure therapy.

Key words  β-blocking agent; chronic heart failure; receptor occupancy; ternary complex model

Chronic heart failure is a pathological condition in which sufficient cardiac output cannot be maintained due to cardiac contractile dysfunction caused by myocardial failure, which produces hemostasis in the lungs and/or systemic venous system, resulting in impairment of daily life.¹ ² Cardiac contractile function regulates ejection of blood, required by peripheral organs, from the left ventricle to aorta, with left ventricular ejection fraction (LVEF) generally employed as its parameter. Cardiac contractile dysfunction is considered to be present when LVEF falls below 40–50% of that in healthy adults.² ³ Moreover, in clinical trials of drugs given to treat heart failure, LVEF increase is used as a parameter to indicate efficacy.

For chronic heart failure therapy, angiotensin-converting enzyme inhibitors, angiotensin 2-receptor antagonists, and β-blocking agents are used.⁴ Although β-blocking agents were previously contraindicated for conventional treatment, because they inhibit cardiac function, their usefulness for chronic heart failure caused by dilated cardiomyopathy, such as mortality decline and improvement of heart failure, was reported in large-scale clinical trials performed in the 1990s. Thus, β-blocking agents are now utilized with positive results.⁴ ⁵ Treatment with one of these agents for chronic heart failure is likely to aggravate heart failure symptoms when a maintenance dose is given from the start of administration. Accordingly, the standard administration method calls for starting with a minimal dose that is one-eighth (0.125%) that of the maximum maintenance dose, with doubling of the dose every 1–2 weeks or longer and setting the final dosage for continued therapy after more than 4 weeks.⁶ ⁷ In such cases, heart rate decrease and bronchoconstriction are adverse effects that should be monitored. In the present study, we performed a theoretical analysis of the efficacy and adverse effects of β-blocking agents used clinically for chronic heart failure for a quantitative comparative evaluation.

MATERIALS AND METHODS

Table 1 shows the initial dose as well as minimum and maximum maintenance doses of oral β-blocking agents presented in the package inserts. Since metoprolol was not approved for treatment of chronic heart failure in Japan at present, the doses were set based on the guidelines and the clinical trial method of other two drugs.⁶ ⁷

In the present study, we compared three different β-blocking agents; carvedilol, bisoprolol, and metoprolol, and their dosages.

Collection of Pharmacokinetic and Pharmacodynamic Parameters Pharmacokinetic and pharmacodynamic param-

Table 1. Oral β-Blocking Agents Used Clinically for Chronic Heart Failure² ⁶ ⁷

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial dose (mg/d)</th>
<th>Maintenance dose (mg/d)</th>
<th>Dose ratio (initial/maximum)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Minimum</td>
<td>Maximum</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>2.5</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>Bisoprolol fumarate</td>
<td>0.625</td>
<td>1.25</td>
<td>5</td>
</tr>
<tr>
<td>Metoprolol tartrate</td>
<td>15</td>
<td>30</td>
<td>120</td>
</tr>
</tbody>
</table>

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eners necessary for the present analysis were extracted from the package insert of each agent, as well as from data used for pharmaceutical product approval applications and past reports in Japanese. The parameters obtained were plasma unbound fraction (fu), area under the plasma concentration time curve (AUC_{0-\infty}), and dissociation constant for the $\beta_1$ and $\beta_2$ receptor ($K_d$).

Calculation of the Average Occupancy of Target Molecules at Time of Repeated Administration of Each Agent On the basis of the obtained data, the steady-state average $\beta_1$ and $\beta_2$ receptor occupancy ($\Phi_{ss1}$ and $\Phi_{ss2}$, respectively) (%) at the time of repeated administration at the doses shown in Table 1 was calculated by using Eqs. 1 and 2.

$$\Phi_{ss1} = \frac{C_{ss1}}{C_{ss1} + K_{d1}} \times 100$$

$$\Phi_{ss2} = \frac{C_{ss2}}{C_{ss2} + K_{d2}} \times 100$$

Where $\Phi_{ss1}$ and $\Phi_{ss2}$ are the average values for $\beta_1$ and $\beta_2$ receptor occupancies (%), and $K_{d1}$ and $K_{d2}$ the dissociation constant (nM) values for the $\beta_1$ and $\beta_2$ receptor. $C_{ss}$ is the steady-state plasma unbound concentration (nM) calculated by using fu and AUC_{0-\infty} at the time of a single administration, and the speculated drug concentration near the receptor. Dose proportionality was confirmed for using the AUC_{0-\infty} of each agent. Moreover, though the active metabolite was confirmed for each agent, it was excluded from analysis as that has been reported to not contribute to efficacy.6-8

Relationship between Average $\beta_1$ Receptor Occupancy and Clinical Efficacy In clinical trials of drugs given to treat heart failure, LVEF increase is used as a parameter to indicate efficacy. Thus, the rate of LVEF increase was calculated as a parameter of clinical efficacy, in which the difference between LVEF at the time of $\beta$-blocking agent administration at the maintenance dose and the level before starting administration was divided by that before the start of administration and expressed as a percentage.9-13 For actual LVEF values, the LVEF values of patients with New York Heart Association (NYHA) Functional Classification grade II or III chronic heart failure were obtained from clinical trial results.

We initially examined the relationship between the calculated $\Phi_{ss}$ value and LVEF increase rate by assuming that the LVEF-improving effect of a $\beta$-blocking agent is obtained by $\beta_1$ receptor blocking on the myocardial cell membrane. When no favorable relationship was observed between them, we speculated that there might be a mechanism that functions directly act on ryanodine receptor 2 in addition to action via the $\beta_1$ receptor in the LVEF-improving effect of $\beta$-blocking agents, as a study of carvedilol reported that its direct action on ryanodine receptor 2 on the sarcoplasmic reticulum membrane was partly involved in clinical efficacy.14) The rate of LVF increase by administration of $\beta$-blocking agents was then analyzed using Eq. 3 in which an additive effect was attained by $\beta_1$ receptor and ryanodine receptor 2.

LVEF increase rate (%) 

$$= E_{max1} \times \frac{\Phi_{ss1}}{100} + E_{max2} \times \frac{\Phi_{ss2}}{100} \times \frac{K_d}{100} \times \frac{\Phi_{ss2}}{100} + K_d \times \frac{1 - \Phi_{ss1}}{100}$$

Where $E_{max1}$ is the maximum efficacy obtained through the $\beta_1$ receptor, $E_{max2}$ the steady-state average for $\beta_1$ receptor occupancy (%), $E_{max2}$ the maximum efficacy obtained by direct action of the agent on ryanodine receptor 2, $\Phi_{ss2}$ the steady-state average inhibition rate (%) of Ca^{2+} release from the sarcoplasmic reticulum mediated by ryanodine receptor 2, $K_d$ the dissociation constant (nM) for the $\beta_1$ receptor, and $K_d$ the dissociation constant (nM) for ryanodine receptor 2 (carvedilol: $K_d$ Car, bisoprolol: $K_d$ Bis, metoprolol: $K_d$ Met). Equation 3 was simultaneously applied using a nonlinear least squares method to the actual value for each agent obtained by $E_{max1}$, $E_{max2}$, and $K_d$. For data analysis, the MLAB software program (Civilized Software Inc.) was used.

Relationship between $\beta$-Blocking Agent Dose and Clinical Efficacy Based on the results of analysis obtained in “Relationship between Average $\beta_1$ Receptor Occupancy and Clinical Efficacy” above, simulated clinical efficacy at the doses shown in Table 1 was examined.

Relationship between $\beta$-Blocking Agent Dose and Adverse Effects By using Eqs. 4 and 5 based on the ternary complex model previously reported by us, the rate of adverse effect, was predicted by using $\Phi_{ss}$ and the rate of average decrease in forced expiratory volume in 1 s (FEV1), which is a respiratory adverse effect, was predicted by using $\Phi_{ss}$. These equations show nonlinear growth graph. In addition, their relationship with dose was evaluated.

$$\Delta HR = 4580\Phi_{ss} + 10^2$$

$$\times \sqrt{21\Phi_{ss}^2 - 4580\Phi_{ss} + 2.5 \times 10^7 - 5 \times 10^4}$$

(4)

$$\Delta FEV_1 = 7690\Phi_{ss} + 10^2$$

$$\times \sqrt{59.1\Phi_{ss}^2 - 1.54 \times 10^7 \Phi_{ss} + 1 \times 10^6 - 1 \times 10^5}$$

(5)
RESULTS

Collection of Pharmacokinetic and Pharmacodynamic Parameters The pharmacokinetic and pharmacodynamic parameters of each agent are shown in Table 2.6–8,16–21) For $K_{d}$, the values reported by Baker, who examined the three agents simultaneously, were used.21)

Calculation of Average Occupation of Target Molecule at Time of Repeated Administration of Each Agent The steady-state plasma concentration ($C_{ss}$), and average $\beta_1$ and $\beta_2$ receptor occupancies ($\Phi_{ss}^{\beta_1}$ and $\Phi_{ss}^{\beta_2}$, respectively) at the time of repeated administration at the initial dose, as well as the minimum and maximum maintenance doses were calculated, with the results shown in Table 3.

For $\Phi_{ss}^{\beta_1}$, bisoprolol and metoprolol showed similar levels (initial dose: 24.0 and 30.9%, minimum maintenance dose: 38.7 and 47.2%, maximum maintenance dose: 71.6 and 78.2%, respectively), whereas carvedilol showed lower levels (10.4, 18.8, 48.1%, respectively). As for $\Phi_{ss}^{\beta_2}$, the levels varied due to the differences of cardio selectivity of each agent. The level was greatest for carvedilol, followed in order by metoprolol and bisoprolol.

Relationship between Average $\beta_1$ Receptor Occupancy and Clinical Efficacy The rates of LVEF increase at a variety of doses of each agent and $\Phi_{ss}^{\beta_1}$ were calculated, with their relationship shown in Fig. 1.6–9–13)

For bisoprolol and carvedilol, the same relationship was noted between $\Phi_{ss}^{\beta_1}$ and LVEF increase rate. Meanwhile for carvedilol, our findings suggested that clinical efficacy was exerted with a lower $\Phi_{ss}^{\beta_1}$ value as compared to the other agents, demonstrating a different aspect of this drug. Accordingly, the actual value for each agent was applied simultaneously to Eq. 3, which takes into consideration the contribution of ryanodine receptor 2 for its analysis. Those results are shown in Fig. 2.5,9–13)

The fitted lines corresponded well with the actual values. Thus, the relationship between $\Phi_{ss}^{\beta_1}$ and clinical efficacy could be analyzed by taking into consideration the direct action on ryanodine receptor 2. Values for the parameters were obtained, as follows: $E_{\text{max}}^{\beta_1}$, 51.0%; $E_{\text{max}}^{\beta_2}$, 20.5%; $K_{d}^{\text{Ry-Carv}}$, 0.0872 nM; $K_{d}^{\text{Ry-Bis}}$, 301.2 nM; $K_{d}^{\text{Ry-Met}}$, 3834 nM. For the increase in LVEF, based on the values for $E_{\text{max}}^{\beta_1}$ and $E_{\text{max}}^{\beta_2}$, it was suggested that the ratio of contribution of the action related to the $\beta_1$ receptor was 71.3%, while that of the direct action on ryanodine receptor 2 was 28.7%. Moreover, the ratio of $K_{d}^{\text{Ry}}$ for the ryanodine receptor to $K_{d}^{\beta_1}$ for the $\beta_1$ receptor of each agent ($K_{d}^{\beta_1}/K_{d}^{\text{Ry}}$) was compared. Our results showed that the affinity of carvedilol for ryanodine receptor 2 was markedly higher as compared to that of the other 2 agents (carvedilol: 20.5, bisoprolol: 0.05, metoprolol: 0.015).

Relationship between Dose and Clinical Efficacy of $\beta$-Blocking Agents The doses and clinical efficacy of the examined $\beta$-blocking agents were simulated on the basis of the parameters obtained, as noted above, with the results shown in Fig. 3.

The rate of LVEF increase at the maintenance dose ranged from 26.5–44.0% for carvedilol (5–20 mg), 20.3–38.8% for bisoprolol (1.25–5 mg), and 24.3–40.9% for metoprolol (30–120 mg), demonstrating that very similar levels of efficacy were obtained at the maintenance dose. That rate associated with the $\beta_1$ receptor of carvedilol ranged from 9.6–24.5% and that with ryanodine receptor 2 ranged from 16.9–19.5%. The ratio of contribution was 36.2–55.7% for the $\beta_1$ receptor and 63.8–44.3% for ryanodine receptor 2. For bisoprolol and metoprolol, the rate of LVEF increase rate associated with ryanodine receptor 2 was markedly lower at 0.6–2.3 and 0.3–1.0%, respectively, while the contribution ratio was 3.0–5.9 and 1.2–2.4%, respectively.

Relationship between Dose and Adverse Effects of $\beta$-Blocking Agents The relationship between the dose and adverse effects of the examined $\beta$-blocking agents, obtained by calculations with Eqs. 4 and 5, are shown in Fig. 4.

The average value for $\Delta$HR at the initial dose was 0.2% for carvedilol, 0.7% for bisoprolol and 1.0% for metoprolol, demonstrating that $\Delta$HR was suppressed at a low level. Meanwhile, the average value for $\Delta$HR at the maximum maintenance dose was 2.2% for carvedilol, 6.0% for bisoprolol, and 8.1% for metoprolol, indicating that the heart rate decreasing effect was lower with carvedilol as compared to metoprolol.

Table 3. Average Unbound Plasma Concentrations ($C_{ss}$), Average $\beta_1$ and $\beta_2$ Receptor Occupancies ($\Phi_{ss}^{\beta_1}$, $\Phi_{ss}^{\beta_2}$) after Administration of Initial, Minimum Maintenance and Maximum Maintenance Dose of Three $\beta$-Blocking Agents Used Clinically for Chronic Heart Failure

<table>
<thead>
<tr>
<th>Drug</th>
<th>$C_{ss}$ (nm)</th>
<th>$\Phi_{ss}^{\beta_1}$ (%)</th>
<th>$\Phi_{ss}^{\beta_2}$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>Minimum</td>
<td>Maximum</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>0.21</td>
<td>0.41</td>
<td>1.6</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>4.7</td>
<td>9.3</td>
<td>37.3</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>25.0</td>
<td>50.1</td>
<td>200.3</td>
</tr>
</tbody>
</table>
and bisoprolol. In addition, the average value for ▲FEV1 at the initial dose was 5.5% for carvedilol, 0.3% for bisoprolol, and 2.1% for metoprolol, while that at the maximum maintenance dose was 25.8, 2.1, and 14.0%, respectively, suggesting that the risk of an induced asthmatic attack was higher for carvedilol, followed in order by metoprolol and bisoprolol.

**DISCUSSION**

In the present study, clinical efficacy and adverse effects of...
the β-blocking agents, carvedilol, bisoprolol, and metoprolol were analyzed theoretically, and then compared quantitatively, for the purpose of determining their proper use for chronic heart failure.

The Фss⁰ value at the usual dose was nearly the same for bisoprolol and metoprolol (24.0–71.6 and 30.9–78.2%, respectively), whereas that for carvedilol was lower (10.4–48.1%). Bisoprolol and metoprolol showed the same relationship between LVEF increase rate and Фss⁰, while our findings suggested that the LVEF increase rate with carvedilol could be attained with a lower Фss⁰ value. These findings support previous reports that noted that a targeted action other than toward the β₁ receptor might be involved in the clinical efficacy of carvedilol. ²²–²⁵

The action mechanism of β-blocking agents is poorly understood. Recent reports have indicated that the major mechanism is correction of the abnormal dynamic state of Ca²⁺ in myocardial cells by indirectly acting on SERCA2a (Ca²⁺-ATPase of cardiac sarcoplasmic reticulum), based on β₁ receptor blocking, to improve contractility. ²²,²⁴–²⁶,²⁹ Moreover, findings in those studies suggested that β-blocking agents might directly act on the ryanodine receptor on the membrane of the cardiac sarcoplasmic reticulum. Another study reported that only carvedilol directly acted on ryanodine receptor 2 to selectively control arrhythmia induced by Ca²⁺ release from the reticulum. ¹⁵ Furthermore, it has been suggested that carvedilol has no inhibitory action toward the involvement of CICR (Ca²⁺-induced Ca²⁺ release) during normal contractions, but acts on arrhythmogenic SOICR (store overload-induced Ca²⁺ release) on ryanodine receptor 2 to selectively inhibit it. ²⁵

In the present study, we constructed a model under the assumption that β-blocking agents exert indirect action through the β₁ receptor and direct action on ryanodine receptor 2, both of which additively exert clinical efficacy (Eq. 3). For clinical efficacy, LVEF increase rate was used as a parameter. In Fig. 2, the fitted lines corresponded well with the actual values. Thus, the relationship between Фss⁰ and clinical efficacy could be analyzed by taking into consideration the direct action on ryanodine receptor 2. Although there is only one LVEF increase rate value for bisoprolol and metoprolol respectively, Eq. 3 was simultaneously applied to the actual one LVEF increase rate value for carvedilol through the β₁ receptor was shown to be 9.6–24.5%, while that attained by direct involvement with ryanodine receptor 2 was 6.9–19.5%. On the other hand, the LVEF increase rate attained by involvement with ryanodine receptor 2 for bisoprolol and metoprolol was remarkably low at 0.6–2.3 and 0.3–1.0%, respectively. Our results clarified, at least theoretically, that only carvedilol produces an effect that directly involves ryanodine receptor 2 at clinical doses.

We also investigated decreases in heart rate and FEV₁ as adverse effects of β-blocking agents using a ternary complex model. Although it was reported that β-blocking agents could improve delayed afterdepolarization and prevent arrhythmia via ryanodine receptor 2, the mechanism of decreasing heart rate via the receptor is not reported. ³³ Thus, we assumed that the ▲HR value could be predicted by using Фss⁰. The average ▲HR value from administration of the initial dose to that of the maximum maintenance dose ranged from 0.2–2.2% for carvedilol, 0.7–6.0% for bisoprolol, and 1.0–8.1% for metoprolol, indicating that carvedilol is less likely to induce a heart rate decrease. The relationship between Фss⁰ and ▲HR value is nonlinear growth. ¹⁵ Thus, if there was a little difference in high Фss⁰ value (maximum dose of bisoprolol: 71.6% and metoprolol: 78.2%), ▲HR value is affected (maximum dose of bisoprolol: 6.0% and metoprolol: 8.1%). These findings were in line with past studies that found carvedilol good for chronic heart failure, as it did not decrease heart rate, and stated that bisoprolol should be used with care in patients with a lower heart rate. ¹³,³² Moreover, average ▲HR at the initial dose was lower by one-eighth to one-eleventh of that at the maximum maintenance dose, demonstrating quantitatively the importance of starting administration at one-eighth of the maximum maintenance dose to prevent aggravation of heart failure. Meanwhile, average ▲FEV₁ from the initial to maximum maintenance dose ranged from 5.5–25.8% for carvedilol, 0.3–2.1% for bisoprolol, and 2.1–14.0% for metoprolol, providing evidence that carvedilol is contraindicated for patients with asthma, as they have a high risk of adverse effects on the respiratory system. These results were considered to support previous reports of the patients with pulmonary disease. ³³,³⁴

The present theoretical findings suggest that carvedilol, bisoprolol, and metoprolol have no differences in regard to clinical efficacy, while their action mechanisms for producing effects vary. Moreover, evidence of adverse effects previously
reported for these agents was theoretically confirmed, suggesting predictable risk. Thus, our results are considered useful for selection of a proper β-blocking agent and its administration at a reasonable dose for successful heart failure therapy.

Conflicts of Interest The authors declare no conflict of interest.

REFERENCES