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 (Φssβ₁ and Φssβ₂) by these drugs. Thereafter, we examined the relationship between Φssβ 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 Φssβ₁ 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 Despite 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.²,⁶,⁷ In the present study, we compared three different β-blocking agents; carvedilol, bisoprolol, and metoprolol, and their dosages.

| Drug                  | Initial dose (mg/d) | Maintenance dose (mg/d) | Dose ratio (initial/maximum) |
|-----------------------|---------------------|-------------------------|----------------------------|
|                       |                     | Minimum                | Maximum                    |                            |
| Carvedilol            | 2.5                 | 5                      | 20                         | 0.125                      |
| Bisoprolol fumarate   | 0.625               | 1.25                   | 5                          | 0.125                      |
| Metoprolol tartrate   | 15                  | 30                     | 120                        | 0.125                      |

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eters 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–∞}), and dissociation constant for the β₁ and β₂ receptor (Kₐ).

**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 β₁ and β₂ receptor occupancy (Φ̂_{ssβ₁} and Φ̂_{ssβ₂}, respectively) (%) at the time of repeated administration at the doses shown in Table 1 was calculated by using Eqs. 1 and 2.

\[
Φ̂_{ssβ₁} = \frac{C_{ss}f}{C_{ss}f + K_{dβ₁}} \times 100
\]

\[
Φ̂_{ssβ₂} = \frac{C_{ss}f}{C_{ss}f + K_{dβ₂}} \times 100
\]

Where Φ̂_{ssβ₁} and Φ̂_{ssβ₂} are the average values for β₁ and β₂ receptor occupancies (%), and K_{dβ₁} and K_{dβ₂} the dissociation constant (nm) values for the β₁ and β₂ receptor. C_{ss}f is the steady-state plasma unbound concentration (nm) calculated by using fu and AUC_{0–∞} at the time of a single administration, and the speculated drug concentration near the receptor. Dose proportionality was confirmed for using the AUC_{0–∞} 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 β₁ 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 β-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 Φ̂_{avg} and LVEF increase rate by assuming that the LVEF-improving effect of a β-blocking agent is obtained by β₁ 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 β₁ receptor in the LVEF-improving effect of β-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 LVEF increase by administration of β-blocking agents was then analyzed using Eq. 3 in which an additive effect was attained by β₁ receptor and ryanodine receptor 2.

\[
\text{LVEF increase rate} (%) = E_{max,β₁} \times \frac{Φ̂_{ssβ₁}}{100} + E_{max,α} \times \frac{I_{SSF}}{100}
\]

\[
\times \frac{K_{a}_{α} \times Φ̂_{ssβ₂}}{100 + K_{dβ₂} \times Φ̂_{ssβ₂}} \times \left\{ \frac{K_{a} \times Φ̂_{ssβ₁}}{100} + K_{dβ₁} \times Φ̂_{ssβ₁} \right\} (3)
\]

Where E_{max,β₁} is the maximum efficacy obtained through the β₁ receptor, Φ̂_{ssβ₁} the steady-state average for β₁ receptor occupancy (%), E_{max,α} the maximum efficacy obtained by direct action of the agent on ryanodine receptor 2, I_{SSF} the steady-state average inhibition rate (%) of Ca²⁺ release from the sarcoplasmic reticulum mediated by ryanodine receptor 2, K_{a} the dissociation constant (nm) for the β₁ receptor, and K_{dβ₂} the dissociation constant (nm) for ryanodine receptor 2 (carvedilol: K_{dβ₂}^{Ry-Car}, bisoprolol: K_{dβ₂}^{Ry-Bis}, metoprolol: K_{dβ₂}^{Ry-Mer}). Equation 3 was simultaneously applied using a nonlinear least squares method to the actual value for each agent obtained by E_{max,β₁}, E_{max,α}, and K_{dβ₂}. For data analysis, the MLAB software program (Civilized Software Inc.) was used.

**Relationship between β-Blocking Agent Dose and Clinical Efficacy**

Based on the results of analysis obtained in “Relationship between Average β₁ Receptor Occupancy and Clinical Efficacy” above, simulated clinical efficacy at the doses shown in Table 1 was examined.

**Relationship between β-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 average decrease in forced expiratory volume in 1 s (FEV₁), which is a respiratory adverse effect, was predicted by using Φ̂_{ssβ₁} and the rate of average decrease in forced expiratory volume in 1 s (FEV₁) in Eq. (5).

\[
\text{▲HR} = 45800Φ̂_{ssβ₁} + 10^2 \times \sqrt{21Φ̂_{ssβ₁}^2 - 45800Φ̂_{ssβ₁} + 2.5 \times 10^7 - 5 \times 10^4} (4)
\]

\[
\text{▲FEV₁} = 7690Φ̂_{ssβ₁} + 10^2 \times \sqrt{59.1Φ̂_{ssβ₁}^2 - 1.54 \times 10^4 Φ̂_{ssβ₁} + 1 \times 10^6 - 1 \times 10^5} (5)
\]
RESULTS

Collection of Pharmacokinetic and Pharmacodynamic Parameters The pharmacokinetic and pharmacodynamic parameters of each agent are shown in Table 2. For Kd, the values reported by Baker, who examined the three agents simultaneously, were used.

Calculation of Average Occupancy of Target Molecule at Time of Repeated Administration of Each Agent The steady-state plasma concentration (Css), and average β1 and β2 receptor occupancies (Φssβ1 and Φssβ2, 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 Φssβ1, 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 Φssβ2, 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 β1 Receptor Occupancy and Clinical Efficacy The rates of LVEF increase at a variety of doses of each agent and Φssβ1 were calculated, with their relationship shown in Fig. 1.

For bisoprolol and carvedilol, the same relationship was noted between Φssβ1 and LVEF increase rate. Meanwhile for carvedilol, our findings suggested that clinical efficacy was exerted with a lower Φssβ1 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.

The fitted lines corresponded well with the actual values. Thus, the relationship between Φssβ1 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: Emax β1, 51.0%; Emax Ry, 20.5%; Kd Ry-Carvedilol, 0.0872 nM; Kd Ry-Bisoprolol, 301.2 nM; Kd Ry-Metoprolol, 3834 nM. For the increase in LVEF, based on the values for Emax β1 and Emax Ry, it was suggested that the ratio of contribution of the action related to the β1 receptor was 71.3%, while that of the direct action on ryanodine receptor 2 was 28.7%. Moreover, the ratio of Kd Ry for the ryanodine receptor to Kd β1 for the β1 receptor of each agent (Kd Ry/Kd β1) 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 β-Blocking Agents The doses and clinical efficacy of the examined β-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 β1 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 β1 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 β-Blocking Agents The relationship between the dose and adverse effects of the examined β-blocking agents, obtained by calculations with Eqs. 4 and 5, are shown in Fig. 4.

The average value for ▲HR at the initial dose was 0.2% for carvedilol, 0.7% for bisoprolol and 1.0% for metoprolol, demonstrating that ▲HR was suppressed at a low level. Meanwhile, the average value for ▲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.
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 Φssb 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 Φssb, while our findings suggested that the LVEF increase rate with carvedilol could be attained with a lower Φssb 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.

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. 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. 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.

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 Φssb 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 bisoprolol and metoprolol, demonstrating quantitatively that carvedilol is less likely to induce a heart rate decrease. For patients with NYHA functional classification class II and III, average LVEF was reported to be 42.8 and 36.3%, respectively, thus it was considered that the percentage increase in LVEF necessary for attaining the target of 50% might be 16.8 and 37.7%, respectively. Those levels agree with the levels obtained in our analysis, indicating that clinical efficacy could be evaluated by using the model constructed in the present study. The LVEF increase rate for carvedilol attained 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. Thus, we assumed that the ▲HR could be predicted by using Φssb. 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 Φssb and ▲HR value is nonlinear growth. Thus, if there was a little difference in high Φssb 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.

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.

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.

**Conflict of Interest** The authors declare no conflict of interest.

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