Evaluation of Drug Efficacy of GLP-1 Receptor Agonists and DPP-4 Inhibitors Based on Target Molecular Binding Occupancy

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Glucagon-like peptide-1 (GLP-1) receptor agonists (liraglutide, exenatide, lixisenatide) have recently been used as anti-diabetes drugs. We examined relationships of the binding occupancy of GLP-1 receptors (Φ) and their clinical efficacy after administration of GLP-1 receptor agonists. Next, by focusing on changes of GLP-1 concentration after administration of dipeptidyl peptidase-4 (DPP-4) inhibitors (vildagliptin, alogliptin, sitagliptin, linagliptin), we analyzed the relationship between Φ and clinical efficacy. Furthermore, using Φ as a common parameter, we compared the clinical efficacy elicited by GLP-1 receptor agonists and DPP-4 inhibitors using a theoretical analysis method. The present results showed that GLP-1 receptor agonists produced their clinical effect at a relatively low level of Φ (1.1–10.7%) at a usual dose. Furthermore, it was suggested that the drugs might achieve their full effect at an extraordinarily low level of Φ. It was also revealed that the Φ value of DPP-4 inhibitors (0.83–1.3%) was at the lower end or lower than that of GLP-1 receptor agonists at a usual dose. Accordingly, the predicted value for hemoglobin A1c (HbA1c) reduction after administration of the GLP-1 receptor agonists was higher than that of DPP-4 inhibitors. We clarified the differences between the therapeutic effects associated with GLP-1 receptor agonists and DPP-4 inhibitors theoretically. Together, the present findings provide a useful methodology for proper usage of GLP-1 receptor agonists and DPP-4 inhibitors.

Key words glucagon-like peptide-1 receptor agonist; pharmacokinetics; pharmacodynamics; dipeptidyl peptidase-4 inhibitor; target molecular binding occupancy

MATERIALS AND METHODS

Relationships of the binding occupancy of GLP-1 receptors and their clinical efficacy after administration of GLP-1 receptor agonists was examined. Next, by focusing on changes of GLP-1 concentration after administration of DPP-4 inhibitors, the relationship between GLP-1 receptor occupancy and clinical efficacy was analyzed. Furthermore, using GLP-1 receptor occupancy as a common parameter, the potency of these drugs was compared in order to evaluate appropriate clinical dosage. Pharmacokinetic and pharmacodynamic data necessary for the present analyses were obtained from published studies, including those related to new drug applications.

Relationship between GLP-1 Receptor Occupancy and Clinical Efficacy after Administration of GLP-1 Receptor Agonists For GLP-1 receptor agonists, in the present study we used liraglutide, exenatide, and lixisenatide, each of which has an established daily dosage regimen. Maximum GLP-1 receptor occupancy (Φ) was calculated by substituting the maximum plasma unbound drug concentration (Cmax) and the dissociation constant of the GLP-1 receptor (Kd) using Eq. 1, as follows.

\[
\Phi = \frac{C_{\text{max}}}{C_{\text{max}} + K_d} \times 100
\]
cebo group and agonist group after 12–14 weeks of pharmacotherapy, was used. We considered that the effect is produced in accordance with the $E_{\text{max}}$ model after GLP-1 receptor agonist binding to the receptor, with $E$ expressed by Eq. 2 using maximum clinical efficacy ($E_{\text{max}}$) and $\Phi$ exhibiting half of $E_{\text{max}}$ ($\Phi_{E_{50}}$), as follows.

$$E = \frac{\Phi}{\Phi + \Phi_{E_{50}}} \times E_{\text{max}} \tag{2}$$

By substituting the values for $\Phi$ and HbA$_{1c}$ reduction after administration of each drug with a various dosage in Eq. 2, $E_{\text{max}}$ and $\Phi_{E_{50}}$ were obtained by fitting with a nonlinear least squares method.

**Relationship between GLP-1 Receptor Occupancy and Clinical Efficacy after Administration of DPP-4 Inhibitors**

Vildagliptin, alogliptin, sitagliptin, and linagliptin, each of which has an established daily dosage regimen, were used as DPP-4 inhibitors. Data obtained in clinical trials regarding plasma GLP-1 concentration and HbA$_{1c}$ reduction after repeated administrations of the subject drugs at a usual dose were obtained.\(^5\)–\(^9\) The value for $\Phi$ was calculated by substituting the GLP-1 concentration ($C_G$) and $K_i$ of GLP-1 ($K_i$; 1500 pM) in Eq. 3.

$$\Phi = \frac{C_G}{C_G + K_i} \times 100 \tag{3}$$

GLP-1 increase ($\Delta C_G$) was calculated based on the DPP-4 inhibition rate ($I$) after repeated administrations of the drugs using Eq. 4, which we previously reported.\(^4\)

$$\Delta C_G = \frac{C_{G,\text{max}} \times 1}{1 + K} - \frac{C_{G,i,\text{max}} \times \left(1 - \frac{I}{100}\right)}{\left(1 - \frac{I}{100}\right) + K} \tag{4}$$

where $C_{G,\text{max}}$ was the maximum level of inactive GLP-1 (20.4 pM), and $K$ was the ratio of DPP-4 activity (0.041).\(^4\)

Then, $C_G$ was obtained by adding the value to the GLP-1 basal concentration under fasted conditions ($C_{G,\text{base}}$: 8.24 pM)\(^1\)–\(^3\) to calculate $\Phi$ with Eq. 3. HbA$_{1c}$ reduction ($E$) was calculated by using $\Delta C_G$ in Eq. 5, which we previously reported.\(^5\)

$$E = 1.14 \times \frac{\Delta C_G}{\Delta C_G + 1.46} \tag{5}$$

Finally, we examined whether the data for $\Phi$ and $E$ after administration of the DPP-4 inhibitors were applicable to the relationship between $\Phi$ and $E$ after administration of the GLP-1 receptor agonists noted above in section 1.

**Comparison of Potency between GLP-1 Receptor Agonists and DPP-4 Inhibitors, and Dosage Evaluations**

HbA$_{1c}$ reduction was determined on the basis of $C_{G,\text{max}}$ after administration of a GLP-1 receptor agonist at the usual dose using Eqs. 1 and 2. The relationship between dose and clinical efficacy was simulated. Moreover, on the basis of $I$ after administration of a DPP-4 inhibitor at the usual dose,\(^5\) HbA$_{1c}$ reduction was determined using Eqs. 4 and 5 for simulating the relationship between dose and efficacy. Based on our findings regarding these relationships, findings for clinical potency of the examined GLP-1 receptor agonists and DPP-4 inhibitors were compared and evaluated. From those results, clinical efficacy in association with changes in the usual dose of the GLP-1 receptor agonists and DPP-4 inhibitors was predicted in order to determine appropriate dosage.

For all data analyses, we employed MLAB (Civilized Software Inc.) program.

**RESULTS**

**Relationship between GLP-1 Receptor Occupancy and Clinical Efficacy after Administration of GLP-1 Receptor Agonists**

Table 1 shows the pharmacokinetic and pharmacodynamic parameters used for calculating $\Phi$ for the GLP-1 receptor agonists,\(^3\)–\(^9\)\(^14\) as well as the calculated values of $\Phi$ after administration of each drug at the doses shown in the table and the values for HbA$_{1c}$ reduction obtained after 12–14 weeks of treatment in clinical trials.\(^5\)–\(^7\)

The $\Phi$ values after administration of the drugs ranged from approximately 1.1–10.7%, whereas those for HbA$_{1c}$ reduction were about 0.73–1.76%. The relationship between $\Phi$ and HbA$_{1c}$ reduction is shown in Fig. 1 together with a fitted line obtained with Eq. 2.

The relationship between $\Phi$ and HbA$_{1c}$ reduction corresponded well with the fitted curve for all of the tested agonists ($r^2=0.91$). The $E_{\text{max}}$ value (mean±standard deviation (S.D.)) obtained was 2.01±0.03%, while $\Phi_{E_{50}}$ was 1.62±0.08%.

**Table 1. Pharmacokinetic and Pharmacodynamic Parameters, $\Phi$, and HbA$_{1c}$ Reduction of GLP-1 Receptor Agonists\(^4\)\(^\text{a}\)\(^\text{,}\)\(^\text{b}\)**

| Drug         | Dose/day | $C_{G,\text{max}}$ (pm) | $f_u$ | $K_i$ (pm) | $\Phi$ (%) | HbA$_{1c}$ reduction (%) |
|--------------|----------|--------------------------|-------|------------|------------|--------------------------|
| Linagliptin  | 0.1 mg   | 2511                     | 1.3   | 0.81       |            |                          |
|              | 0.3 mg   | 7691                     | 3.9   | 1.16       |            |                          |
|              | 0.6 mg   | 15269                    | 0.008 | 7.5        | 1.59       |                          |
|              | 0.9 mg\(^c\) | 22414                 | 10.7  | 1.76       |            |                          |
| Exenatide    | 5 µg     | 12.8                     | 1.4   | 0.95       |            |                          |
|              | 10 µg\(^c\) | 28.9                    | 3.1   | 1.34       |            |                          |
|              | 20 µg\(^c\) | 68.3                    | 7.1   | 1.52       |            |                          |
| Lixisenatide | 20 µg\(^c\) | 33.6                    | 0.45  | 1.1        | 0.73       |                          |

\(\text{a)}\) Usual dose.
Relationship between GLP-1 Receptor Occupancy and Clinical Efficacy after Administration of DPP-4 Inhibitors

Of the tested DPP-4 inhibitors, clinical trial data for the GLP-1 concentration in plasma and HbA\(_1c\) reduction after repeated administrations at a usual dose could be obtained only for vildagliptin and alogliptin, with those values shown in Table 2.\(^{10-13}\) As for the 4 drugs examined, \(\Delta C_G\) calculated from the DPP-4 inhibition rate (\(I\))\(^4\) and \(\Phi\) also calculated from that, as well as HbA\(_1c\) reduction are shown together in Table 2. Following administration of each drug at a usual dose, the \(\Phi\) value ranged from approximately 0.83–1.3%, while HbA\(_1c\) reduction was about 0.82–1.1%. The values for both were at the lower limit or lower as compared to those for the GLP-1 receptor agonists.

Figure 2 shows \(\Phi\) and HbA\(_1c\) reduction values after DPP-4 inhibitor administration at the usual dose, and plotted with the fitted line from Fig. 1. The \(\Phi\) and HbA\(_1c\) reduction values fit well with that line (\(r^2=0.53\)).

### Table 2. Pharmacokinetic and Pharmacodynamic Parameters, \(\Phi\), and HbA\(_1c\) Reduction of DPP-4 Inhibitors\(^{10-13}\)

| Drug     | Dose/day (mg/d) | \(I_{ss}\) (%) | \(C_{Gbase}\) (pM) | \(\Delta C_G\) (pM) | \(\Phi\) (%) | HbA\(_1c\) reduction (%) |
|----------|-----------------|----------------|---------------------|---------------------|--------------|--------------------------|
| Vildagliptin | 100\(^a\)        | 97.5           | 12                  | 1.3                 | 1.0          |
|           |                 |                |                     | 1.2\(^b\)           | 1.1\(^c\)    |
| Alogliptin | 25\(^c\)         | 90.4           | 5.3                 | 0.89                | 0.89         |
|           |                 |                |                     | 0.90\(^d\)           | 0.82\(^e\) |
| Sitagliptin | 75\(^c\)         | 90.6           | 5.4                 | 0.90                | 0.89         |
| Linagliptin | 5\(^c\)          | 87.9           | 4.4                 | 0.83                | 0.85         |

\(^a\) Usual dose. \(^b\) Basal concentration of GLP-1 under fasted conditions. \(^c\) Actual value.

**Fig. 2.** Relationship between \(\Phi\) and HbA\(_1c\) Reduction of DPP-4 Inhibitors

*Solid line* indicates simulated line, *open symbols* indicate actual values, *closed symbols* indicate predicted values, \(r^2=0.53\).

**Fig. 3.** Relationship between Dose and HbA\(_1c\) Reduction of GLP-1 Receptor Agonists (A) and DPP-4 Inhibitors (B)

*Gray area* indicate usual dose.

**DISCUSSION**

When the pharmacological effect is mediated by the target molecule, it is important to quantitatively examine the relationship of the target drug near the site of action and its bind-
ing to that molecule. In our previous studies, we clarified that occupancy for the target molecule can be useful as a parameter for evaluating clinical efficacy.\(^{15,16}\) As for GLP-1 receptor agonists, those examined in the present study exhibit a clinical effect after binding to the GLP-1 receptor, thus we considered that our analysis based on GLP-1 receptor occupancy rate would be applicable. DPP-4 inhibitors are considered to elicit their clinical effect by GLP-1, which is increased by selective DPP-4 inhibition. Accordingly, we considered that a quantitative comparison with the present GLP-1 receptor agonists could be made by use of a similar analysis method.

For calculating the GLP-1 receptor occupancy of the agonists, we speculated that the drug concentration near the receptor is equivalent to the plasma unbound drug concentration. \(K_i\) values, used for calculating \(\Phi\), were collected from the same trial results in order to prevent diffusion caused by differences in trial conditions. The \(K_i\) value for liraglutide was set to be comparable to the value for GLP-1, as it has a 97% homology with GLP-1 and showed an equal effect with GLP-1 in an in vitro trial, though no reported value was available.\(^{17}\)

Assuming that the number of GLP-1 receptors is not change, at over dose \((C_{\text{max}}>>K_i)\), \(\Phi\) becomes an upper limit (100%) theoretically from Eq. 1. Since the calculated \(\Phi\) value of each drug at a usual dose ranged from 1.1–10.7%, we considered that GLP-1 receptor agonists elicit their clinical effect at an extraordinarily low level of occupancy.

For examining the relationship between GLP-1 receptor occupancy and clinical efficacy, we used HbA\(_{1c}\) reduction after 12 to 14 weeks of treatment as a parameter for clinical effect. At over dose, it is thought that HbA\(_{1c}\) reduction as well as \(\Phi\) is high level. However, HbA\(_{1c}\) is not to be lower than zero. Therefore, Eq. 2 which has upper limit of HbA\(_{1c}\) reduction \((E_{\text{max}})\) is valid to explain the relationship between \(\Phi\) and HbA\(_{1c}\) reduction. When collecting related clinical trial data, we confirmed that there was not a great difference in patient background findings. Our analysis showed that the relationship between \(\Phi\) and HbA\(_{1c}\) reduction fit well with the theoretically constructed model \((r^2=0.91)\). Thus, we propose that \(\Phi\) can be used as a common parameter for the clinical efficacy of GLP-1 receptor agonists (Fig. 1). Moreover, since the \(\Phi_{E50}\) value was 1.62±0.08%, it is suggested that the drugs might achieve their full effect at an extraordinarily low level of occupancy. It is reported that the average receptor occupancy rate of agonist at usual dose is about 1–2%.\(^{15}\) Thus, in case of agonist, the low receptor occupancy rate is effective.

For the purpose of comparing the present GLP-1 receptor agonists with the DPP-4 inhibitors, \(\Phi\) was calculated similarly for the DPP-4 inhibitors. The \(\Phi\) value ranged from 0.83–1.3% when each drug was given at a usual dose, which was at the lower end or lower than that of the GLP-1 receptor agonists. The relationship between the \(\Phi\) value of the DPP-4 inhibitors and HbA\(_{1c}\) reduction after DPP-4 inhibitor administration at a usual dose corresponded well with the fitted line in Fig. 1 \((r^2=0.53)\), suggesting that the \(\Phi\) value for a GLP-1 receptor can be used to predict HbA\(_{1c}\) reduction for a DPP-4 inhibitor (Fig. 2).

In Fig. 3A, we showed the relationship between Dose and HbA\(_{1c}\) reduction of GLP-1 receptor agonists on the basis of the estimated \(E_{\text{max}}\) and \(\Phi_{E50}\) using Eqs. 1 and 2. On the other hand, in Fig. 3B, we showed the relationship of DPP-4 inhibitors on the basis of the estimated \(f\) after administration of a DPP-4 inhibitor at the usual dose using Eqs. 4 and 5. Therefore, Figs. 3A and B are the conceptual graphs of clinical efficacy of both drugs. The predicted value for HbA\(_{1c}\) reduction after administration of the GLP-1 receptor agonists at a usual dose ranged from 1.73–1.98% (Fig. 3A). Meanwhile, that value after administration of the DPP-4 inhibitors at a usual dose was from 0.77–1.0% (Fig. 3B). Accordingly, we concluded that the HbA\(_{1c}\) reducing effect was higher with the GLP-1 receptor agonists than with the DPP-4 inhibitors. In addition, the \(E_{\text{max}}\) value calculated by use of Eqs. 1 and 2 was 2.01% for the GLP-1 receptor agonists, and that calculated by Eqs. 3 and 4 was 1.06% for the DPP-4 inhibitors, thus it was theoretically suggested that DPP-4 inhibitors could not equal the effect of the GLP-1 receptor agonists. Moreover, for both the GLP-1 receptor agonists and DPP-4 inhibitors, the usual dose was set at a level for attaining maximum effect. Our results clarified that an intensification of the effect should not be expected even if the dose is increased over the usual dose, whereas the effect will become drastically lower when the dose is reduced.

GLP-1 enhanced satiety and reduced energy intake\(^{8,19}\) and thus treatment with GLP-1 receptor agonists leads to weight loss.\(^{2,20}\) It is thought that the appetite suppressing effect leads to HbA\(_{1c}\) reduction. Although we did not analyze the appetite suppressing effect in this study, it is thought that we evaluated HbA\(_{1c}\) reduction covering the appetite suppressing effect using \(\Phi\) calculated from serum drug concentration.

The present results show that GLP-1 receptor agonists produce their clinical effect at a relatively low level of GLP-1 receptor occupancy \((\Phi)\), suggesting that \(\Phi\) can be utilized as a common parameter for evaluating clinical efficacy irrespective of the kind of drugs being examined. At this point, when this study is applied to the individual patient, based on this study and data of the patient, it would be possible to individually determine the parameters and evaluate the clinical efficacy. Furthermore, they suggest that a comparison of the differences in clinical efficacy between GLP-1 receptor agonists and DPP-4 inhibitors on the basis of \(\Phi\) allows for quantitative evaluation of clinical efficacy. It was also revealed that the examined GLP-1 receptor agonists have a higher HbA\(_{1c}\) reducing effect than the DPP-4 inhibitors when administered at a usual clinical dose. Together, the present findings provide a useful methodology for proper usage of GLP-1 receptor agonists and DPP-4 inhibitors.

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

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