Pharmacokinetics and Pharmacodynamics of Glimepiride in Type 2 Diabetic Patients: Compared Effects of Once- versus Twice-daily Dosing

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Abstract. To compare the pharmacokinetic and pharmacodynamic effects of glimepiride between once- and twice-daily dosing in type 2 diabetic patients. Eight Japanese type 2 diabetic patients, who had been treated with 2 mg glimepiride alone over 4 weeks (age 40–70, body mass index ≤25 kg/m^2, hemoglobin A1C<8.0%), were randomly assigned to the crossover study with glimepiride 2 mg once-daily and 1 mg twice-daily for 4 weeks for each regime. Serum concentrations of glimepiride, plasma glucose, insulin and C-peptide were measured over 24 h at the fixed time intervals on the last day of each crossover period, and HbA1C was measured at the same day. Pharmacokinetic profiles in two regimens were different to each others; a single peak of serum glimepiride concentration was observed in once-daily, and double peaks in twice-daily dosing. Drug concentration increased immediately, and peaked at 2 h after administration irrespective of dosage. Cmax value in once-daily dose was higher than those in twice-daily doses. AUC values were not different between two regimens. Pharmacodynamic profiles for plasma glucose, serum insulin and C-peptide showed no statistically significant differences between two regimens, and parameters were not different each other. Analyses of adverse events and laboratory data demonstrated a favorable safety profile of glimepiride. The present results suggest that glimepiride may be suitable for once-daily dosing with respect to clinical usefulness.

Key words: Glimepiride, Type 2 diabetes, Pharmacokinetics, Pharmacodynamics

GLIMEPIRIDE, a new generation sulfonylurea, has been widely used in the world including Japan. In comparison with conventional sulfonylurea drugs, glimepiride has several benefits: rapid and complete absorption after oral administration, a lower dose, long duration of action, and possible insulin-sensitizing effect [1–3]. In addition, the previous clinical studies demonstrated that glimepiride once-daily dose, which is a common usage of this agent in Europe and the US, provided a good glycemic control of type 2 diabetes as well as twice-daily doses [4]. Sulfonylurea drugs are preferred as the first choice rather than other oral antidiabetic agents to treat type 2 diabetic patients in Japan, probably due to the lower potency of insulin release from the pancreas in Japanese subjects compared with Caucasian. On the other hand, the usual daily dosage of conventional sulfonylurea drugs in Japanese patients is much less than that in Caucasian patients. These facts strongly suggest that the pathophysiology of type 2 diabetes mellitus and the sensitivity to sulfonylurea drugs are different between the two populations. It is of interest, however, that the usual daily dose range of glimepiride (~1–4 mg) is not different between Japan and Europe/US, and that an average daily dose is ~2–3 mg in Japan (unpublished data). In Japan a twice-daily dosing of sulfonylureas including
glimepiride is more common than once-daily dose without any significant evidence.

In the present study, we attempted to investigate the pharmacokinetic and pharmacodynamic properties of once- or twice-daily dose of glimepiride in randomized, 2-phase crossover study in Japanese type 2 diabetic patients. This is the first report to demonstrate the correlation between pharmacokinetics and pharmacodynamics of glimepiride in type 2 diabetic patients using the crossover-study protocol.

**Research design and Methods**

The study was conducted as a single center, randomized, two-period, crossover trial in Kawasaki Medical School Hospital. The study protocol was approved by the institutional review boards at the Ethics Committee of Kawasaki Medical School Hospital, and the study was carried out according to the principles of Declaration of Helsinki. Written informed consent was obtained from all patients.

**Subjects**

Outpatients with type 2 diabetes mellitus were recruited according to the following inclusion criteria: treated with 2 mg glimepiride alone over 4 weeks duration, age 40–70 years, weighing less than 25 kg/m$^2$ of body mass index, and HbA$_{1C}$ less than 8.0%. All subjects were free of concomitant illness such as heart disease, hepatic (serum alanine aminotransferase more than the upper limit of normal) or renal (serum creatinine more than the upper limit of normal) dysfunction. None of the patients had a history of severe hypoglycemia, active proliferative retinopathy or clinically significant neuropathy. Concomitant medications without hypoglycemic agents were permitted if the dose was stabilized for one month and during the study.

**Study design**

Prior to the randomized 2-period crossover study, patients were treated with once-daily 2 mg of glimepiride in order to stabilize metabolic control over 3 to 5 weeks as a screening period. After screening period, subjects were randomly allocated to once-daily dose regimen with 2 mg of glimepiride before breakfast or twice-daily with 1 mg before breakfast and dinner, and were treated for 4 weeks (the first-period of crossover). Then, the regimen was reversed from that used in the first-period. Patients were treated by the new regimen for 4 weeks (the second-period of crossover). During the study period, they were asked to maintain a fixed calorie diet, which was calculated individually based on the ideal body weight and physical activity of each patient. They were also asked to fix meal times at 8 am for breakfast, midday for lunch and 6 pm for dinner.

Subjects were admitted one day before the final day of each period of the study. On the next day, 24-h profiles for serum glimepiride concentration, plasma glucose, serum insulin and C-peptide levels were analyzed. For the determination of HbA$_{1C}$ and other biochemical parameters, blood was drawn before breakfast. For the pharmacokinetic experiment, serum glimepiride concentrations were measured 14 times over 24 hours. For pharmacodynamic experiment, plasma glucose levels 19 times, and serum insulin and C-peptide levels were also measured 15 times. During experiments, each subject was fed an individually fixed-calorie diet three times, which they were asked to maintain before admission. Except for the fixed meals, no food or drink other than water was permitted until completion of studies.

**Analytical procedures**

Plasma glucose and HbA$_{1C}$ were measured by standard laboratory methods. Insulin and C-peptide levels were measured by enzyme immunoassay method and glimepiride concentrations were analyzed by liquid chromatography-tandem mass spectrometry method (SRL, Inc., Tokyo, Japan), using of the Hitachi L-Series (Hitachi, Tokyo, Japan). Glimepiride from 1 ml plasma with internal standard was extracted by same volume of diethyl ether and 1-fluoro 2,4-dinitrobenzene, and was dried. Standards of glimepiride and patient samples were separated using Spherisorb ODS 2 column (5 µm, 4.6 mm i.d. × 125 mm, Waters, Milford, MA, USA) and a mobile phase consisting of acetonitrile and perchlorate (1 : 1) were used. Blood concentration of glimepiride was calculated by measuring peak area. The quantification limit was 12.5 to 200 ng/mL. Interday coefficients of variation for glimepiride were 9.0% at 12.5 ng/mL, 3.7% at 50.0 ng/mL, and 5.0% at 200.0 ng/mL (n = 15). Intraday coefficients of variation for glimepiride were 2.3% at 12.5 ng/mL, 2.6% at 50.0 ng/mL, and 1.6% at 200.0 ng/mL.
Pharmacokinetic parameters of glimepiride were characterized by peak concentration in serum ($C_{\text{max}}$), time to $C_{\text{max}}$ ($T_{\text{max}}$), and elimination half-life ($T_{1/2}$), and the area under glimepiride concentration versus time curve (AUC) was calculated for different time periods under the individual profiles by means of the trapezoidal rule. Pharmacodynamic measures for glucose, insulin and C-peptide concentrations were also evaluated as in the same manner as in the pharmacokinetic analyses.

**Statistical analysis**

All data from the two study groups were expressed as mean ± standard error of the mean (SEM). Statistical comparisons were performed between the two groups was determined by Mann-Whitney U test. Statistical significance was accepted when $P$ value was less than 0.05.

**Results**

A total of seven patients were screened for preparation in this study, and eight patients with written informed consent (2 female and 6 male) were enrolled and randomly allocated to one of the 2 groups according to the protocol; one half to once-daily dose the regimen and the remaining 4 subjects to twice-daily doses. All subjects completed the study for the 8 weeks. The baseline characteristics of the 8 subjects are shown in Table 1. The age was 63.5 ± 1.8 years, and the duration of diabetes was 14.6 ± 1.8 years. Baseline HbA$_{1C}$ was 6.9 ± 0.2% and body mass index was 22.9 ± 1.1 kg/m$^2$.

**Pharmacokinetics**

As shown in Fig. 1, the pharmacokinetic profiles in two groups were different each other; a single peak of serum glimepiride concentrations was observed in once-daily dose group, and double peaks in twice-daily dose group. Glimepiride concentrations increased immediately, and peaked around 2 h after administration in both once-daily and twice-daily groups. $C_{\text{max}}$ value in once-daily dose was significantly higher than those in twice-daily doses only for the second peak ($P = 0.055$ for the first peak and $P = 0.005$ for the second peak, Table 2). $C_{\text{max}}$ of the second peak of glimepiride concentration in twice-daily dosing group observed in the evening appeared to be lower than that of the first peak observed in the morning, but not significant statistically ($P = 0.215$). AUC values were not different between two groups.

**Pharmacodynamics**

The 24-h glucose profiles were similar in once-daily dose and twice-daily doses of glimepiride as shown in Fig. 2. Fasting plasma glucose concentration, post-prandial glucose concentration, mean plasma glucose and AUC value for plasma glucose were not different
between the two groups (Table 3). The 24-h insulin profiles showed 3 peaks of serum insulin level associated with meals in both two groups (Fig. 3A). Peak values of insulin in twice-daily doses seemed to be lower than those in once-daily dose group, whereas there were no statistically significant differences in fasting or postprandial insulin levels in two groups. When the C-peptide profiles between two groups were compared, there were also no significant differences at any points measured (Fig. 3B). The 24-h total insulin and C-peptide values were not different between two groups. HbA1c values at the end of the study also were not different in both groups (Table 3).

### Safety

All patients included in this study were evaluated with regard to safety. No case with hypoglycemia was observed, and no adverse events were related to the treatment with glimepiride, suggesting a favorable safety profile of this drug.

### Discussion

This crossover study was initiated to compare the pharmacological effects of glimepiride between once-and twice-daily dosing based on the comparative analyses of both pharmacokinetics and pharmacodynamics of these two regimens. Our study clearly demonstrated that once- and twice-daily dosing of glimepiride provided different pharmacokinetic profiles each other, but were equally effective in regulating plasma glucose, serum insulin and C-peptide levels in patients with type 2 diabetes. The Tmax values observed in this study were not different from those in normal subjects and in diabetic patients reported previously [5–7]. A recommended daily dosage of glimepiride in Japanese subjects is ~1–4 mg, and the majority of patients treated with this drug receive ~2–3 mg daily. Thus the dosage used is appropriate in the study using Japanese subjects.

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**Table 3. Pharmacodynamic parameters**

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<thead>
<tr>
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<th>Once-daily</th>
<th>Twice-daily</th>
<th>P</th>
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<tbody>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.0 ± 1.0</td>
<td>22.9 ± 1.0</td>
<td>0.792</td>
</tr>
<tr>
<td>24-hr mean PG (mg/dL)</td>
<td>199.8 ± 17.2</td>
<td>195.3 ± 15.0</td>
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</tr>
<tr>
<td>PG AUC (mg h/dL)</td>
<td>4775 ± 400</td>
<td>4101 ± 269</td>
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<tr>
<td>HbA1c (%)</td>
<td>6.9 ± 0.2</td>
<td>7.1 ± 0.1</td>
<td>0.958</td>
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<tr>
<td>ΣIRI (µU/mL)</td>
<td>226.9 ± 25.9</td>
<td>200.1 ± 23.4</td>
<td>0.294</td>
</tr>
<tr>
<td>ΣCPR (ng/mL)</td>
<td>54.9 ± 2.1</td>
<td>51.8 ± 2.4</td>
<td>0.294</td>
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</table>

Parameters at the last day of each crossover period in 8 patients. Results are shown as mean ± SEM.
Several observations using relatively higher dosage of glimepiride also concluded that pharmacodynamic effects of this drug given in once- and twice-daily to diabetic patients were comparable. Rosenstock et al. reported the comparable effect of once-daily dose of glimepiride (8 mg or 16 mg) with twice-daily doses (4 mg BID or 8 mg BID) in a double-blind placebo-controlled study of American (ethnicity unknown) type 2 diabetic patients [4]. They concluded that there were no meaningful differences in glycemic variables such as fasting plasma glucose, postprandial glucose, HbA1c value, and serum insulin and C-peptide levels between once- and twice-daily dosing. Furthermore, Sonnenberg et al. demonstrated that 24 h mean glucose concentrations showed a slightly greater decrease for 6 mg twice-daily, compared with once-daily dose, but that clinically both regimens were effective in promoting glycemic control [8].

It is of interest that insulinotropic effects were not different between once- and twice-daily doses of glimepiride, whereas a distinct difference in 24-h pharmacokinetic profiles was observed between the two regimens. The relationship between pharmacokinetic and pharmacodynamic actions for sulfonylurea drugs has been investigated [9, 10]. When sulfonylurea drugs were administered, the correlation between drug concentration and its effect on insulin level was only apparent with the first 3–5 h after drug administration [10]. In the present study, the first peak of glimepiride concentration in blood was consistent with the peak of serum insulin level after breakfast, but the peak of serum insulin after dinner was not related with drug concentration in blood. Our results were similar to those reported by them. These findings indicated that the pharmacodynamic action of sulfonylureas appear to be independent of their serum concentrations. Several possible reasons may be cited for this observation. Changes in binding of the highly plasma protein bound drug [11] or slow dissociation from the receptor at the ATP-regulated K+-channel [13] may be related in deviation of drug concentration in serum and effect. This phenomenon observed in sulfonylurea drugs is clearly different from that observed in nateglinide, a rapid-onset and short-acting insulin secretagogue [13–15].

Medicated compliance is a common problem among diabetic patients [16, 17]. Once-daily dose compared with more frequent dosing regimen promises to improve compliance among patients with NIDDM [18, 19]. Paes et al. demonstrated that compliance of antidiabetic drugs in three times-daily dosing was reduced 50% compared with once-daily dosing [20]. Thus the present results may provide evidence for the superiority of once-daily dose in terms of increment of compliance.

In summary, this crossover study demonstrates that the pharmacodynamic and safety profiles in once-daily dose of glimepiride in type 2 diabetic patients are not different from those in twice-daily dosing. Once-daily dosing is more suitable for the type 2 diabetic patients treated with glimepiride.

References