Effect of Combination Therapy of a Rapid-Acting Insulin Secretagogue (Glinide) with Premixed Insulin in Type 2 Diabetes Mellitus

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Abstract

Aim The effect of rapid-acting insulin secretagogues (glinides) on glycemic control when included with insulin therapy for type 2 diabetes remains uncertain. To examine this, we added glinide once a day to twice daily injections of premixed insulin.

Research Design and Methods Seventy-four type 2 diabetic patients, taking twice daily injections of premixed insulin and whose diabetic control was stable, were registered at 6 independent institutions. After a 3-month observation period, 60 patients were administered 10 mg mitiglinide or 90 mg nateglinide at lunchtime without changing their insulin regimen. After 12 weeks, administration of glinide was discontinued and observation was continued. HbA1c levels were measured at the start of glinide administration, after 12 weeks of glinide, and at 12 weeks after discontinuation.

Results HbA1c improved from 7.72±0.66% to 7.55±0.71% (p<0.01) at Week 12 of glinide administration. Twelve weeks after discontinuation, HbA1c returned to the baseline level (7.72±0.81%).

Conclusion This study indicates that the addition of glinide once a day at lunchtime to twice daily injections of premixed insulin is effective for the treatment of type 2 diabetes.

Key words: glinide, insulin treatment, glycemic control

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Introduction

A delay in bolus insulin secretion is a characteristic of early-stage type 2 diabetic patients. Its improvement by any kind of treatment is important for recovery of physiologic insulin concentration, obtaining tight glycemic control, delaying the disease process, and preventing diabetic complications.

Although intensive insulin treatment resembles the physiologic insulin secretion pattern, preventing diabetic complications (1-3), many type 2 diabetic patients prefer more “convenient” treatment, such as twice daily injections of premixed insulin. In particular, elderly type 2 diabetic patients may be unable to inject insulin 4 or 5 times per day and, even in younger patients, it is sometimes difficult to manage due to environment associated with an intense working day.

On the other hand, with twice daily treatment with premixed insulin, some type 2 diabetic patients complain of hypoglycemia before lunch, necessitating a reduction in the insulin dose at breakfast. Reducing the insulin dosage at breakfast, however, causes an increase in evening plasma glucose levels in some patients; indicating the limitation of this insulin regimen.

The addition of glinide, a novel rapid-acting insulin secretagogue, at lunchtime is expected to solve this problem. Therefore, in the present study, we investigated the thera-
Table 1. Clinical Characteristics of the Patients in this Study

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Enrolled</th>
<th>Mitiglinide</th>
<th>Nateglinide</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (M/F)</td>
<td>74 (44/30)</td>
<td>60 (37/23)</td>
<td>30 (16/14)</td>
<td>30 (21/9)</td>
</tr>
<tr>
<td>Age (y/o)</td>
<td>64.6 ± 9.9</td>
<td>64.4 ± 10.5</td>
<td>64.1 ± 10.8</td>
<td>64.7 ± 10.4</td>
</tr>
<tr>
<td>Disease duration (y)</td>
<td>18.3 ± 9.7</td>
<td>18.8 ± 9.7</td>
<td>18.5 ± 11.6</td>
<td>19.0 ± 7.6</td>
</tr>
<tr>
<td>BMI</td>
<td>24.3 ± 3.6</td>
<td>24.1 ± 3.4</td>
<td>23.9 ± 3.7</td>
<td>24.3 ± 3.2</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.65 ± 0.72</td>
<td>7.72 ± 0.66</td>
<td>7.75 ± 0.60</td>
<td>7.70 ± 0.73</td>
</tr>
<tr>
<td>Insulin dose (U/kg)</td>
<td>0.39 ± 0.16</td>
<td>0.38 ± 0.16</td>
<td>0.41 ± 0.17</td>
<td>0.35 ± 0.15</td>
</tr>
<tr>
<td>Human insulin/ Insulin analogue</td>
<td>49/25</td>
<td>44/16</td>
<td>17/13</td>
<td>27/3</td>
</tr>
</tbody>
</table>

After 12 weeks of glinide administration, glinide was discontinued and the patients were followed for a further 12 weeks. Body mass index (BMI), blood pressure, post breakfast plasma glucose, HbA1c level, and lipid profiles (LDL-C, TG, HDL-C) were evaluated at registration, 12 weeks after administration of glinide, and 12 weeks after discontinuation. Serum 1,5-anhydroglucitol (1,5-AG) levels were also measured in some of the enrolled patients (n=34). All patients self-monitored capillary blood glucose levels using a Gluestest-ace meter (Arkray Co., Kyoto, Japan) or a Medisafe-Mini meter (Terumo Co., Tokyo, Japan) to confirm any episodes of hypoglycemia. Hypoglycemia was defined as plasma glucose 60 mg/dl, or less, with or without hypoglycemic symptoms. The insulin regimen, insulin dose, antihypertensive drugs or antihyperlipidemic agents, remained unchanged throughout the study period.

Study design

This study was performed as a multi-centered trial in Keio University Hospital (KU), Kitasato Institute Hospital (KI), Saiseikai Central Hospital (SC), Nippon Kokan Hospital (NK), Hamamatsu Red Cross Hospital (HR), and Tokyo Metropolitan Ohtsuka Hospital (MO), Japan. Patients who had been using premixed human insulin (30% regular insulin and 70% NPH insulin) or a premixed insulin analogue (30% insulin aspart and 70% protamine crystallized insulin aspart) twice daily (at breakfast and in the evening) for more than 3 consecutive months and whose HbA1c level was between 6.5 and 8.0% were eligible for this study. After a 12-week observation period, 60 patients with an HbA1c level of over 6.5% and a change in HbA1c from registration within 1.0% were enrolled and were placed on a diet and exercise regimen throughout the study period. Patients who met these criteria were then given 10 mg mitiglinide or 90 mg nateglinide at lunchtime for 12 weeks. Patients at KU and KI were randomly assigned to either of the two agents by computer, at SC and MO, patients were administered 10 mg mitiglinide, and at NK and HR they received 90 mg nateglinide. In Japan, 90 mg of nateglinide and 10 mg of mitiglinide are recommended as a regular mealtime dosage and recognized as clinically equivalent.

After 12 weeks of glinide administration, glinide was discontinued and the patients were followed for a further 12 weeks. Body mass index (BMI), blood pressure, post breakfast plasma glucose, HbA1c level, and lipid profiles (LDL-C, TG, HDL-C) were evaluated at registration, 12 weeks after administration of glinide, and 12 weeks after discontinuation. Serum 1,5-anhydroglucitol (1,5-AG) levels were also measured in some of the enrolled patients (n=34). All patients self-monitored capillary blood glucose levels using a Gluestest-ace meter (Arkray Co., Kyoto, Japan) or a Medisafe-Mini meter (Terumo Co., Tokyo, Japan) to confirm any episodes of hypoglycemia. Hypoglycemia was defined as plasma glucose 60 mg/dl, or less, with or without hypoglycemic symptoms. The insulin regimen, insulin dose, antihypertensive drugs or antihyperlipidemic agents, remained unchanged throughout the study period.

Statistical analyses

For statistical analysis, StatView (version 5.01; SAS Institute, Cary, NC) was used. A paired or unpaired t-test was used for comparison where appropriate, and p<0.01 was considered statistically significant to avoid an increase in alpha errors. All numerical values are expressed as means ± S.D. All patients gave informed consent and the study protocol was approved by institutional review board.

Results

Of the 74 patients who were registered during the entry period from July 2004 to June 2005, 14 were excluded because of an excess change in HbA1c (>1.0%) during the observation period, leaving 60 patients who were enrolled. Of
these, three patients had HbA1c levels between 6.5% and 7.0% and satisfied the glycemic control recommendations of the American Diabetes Association (4) at baseline. Thirty patients were given 10 mg mitiglinide and the remaining 30 were given 90 mg nateglinide to be administered once daily at lunchtime. Baseline characteristics are shown in Table 1. Among the 60 patients, 44 were using premixed human insulin and 16 were using a premixed insulin analogue.

Adding the glinide treatment at lunchtime to twice daily injections of premixed insulin caused a significant decrease in HbA1c levels from 7.72±0.66% to 7.55±0.71% (p<0.01). Moreover, discontinuation of glinide treatment resulted in a return to the baseline HbA1c level (from 7.55±0.71% to 7.72±0.81%; p<0.005) (Fig. 1a). The HbA1c level of 11 patients was less than 7.0% and satisfied the glycemic control recommendations of the American Diabetes Association (4) and three patients had HbA1c levels less than 6.5% and satisfied the “good” criteria of the Japanese Diabetes Society (5) at 12 weeks after glinide treatment. The changes in HbA1c levels between baseline and Week 12 of glinide administration did not differ between the groups taking 10 mg mitiglinide (n=30) and 90 mg nateglinide (n=30) (-0.23% and -0.13%, respectively, N.S.), and therefore, the data were combined. In addition, the changes in HbA1c levels between baseline and Week 12 of glinide administration did not differ between the patients taking premixed human insulin and those taking premixed insulin analogue (-0.17% and -0.18%, respectively, N.S.), again allowing combination of the data.

No significant changes in postprandial plasma glucose levels (1 to 3 hours after breakfast) were seen throughout the study period (Fig. 1b). Moreover, BMI, blood pressure, and lipid profiles did not change throughout the study period (Table 2). 1,5-AG tended to increase after administration of glinide (p=0.07), and decrease after discontinuation (p=0.05), although these changes did not reach statistical significance (Fig. 1c).

The frequency of hypoglycemic episodes did not differ before and after administration of the glinide (9 before administration, 10 during and 8 after discontinuation). No episode of serious hypoglycemia, requiring assistance, occurred during the study period.

Discussion

Many reports have documented combination therapy regimens with insulin and oral hypoglycemic agents. Yki-Jarvinen (6) suggested in a review article that combination therapy allows the use of less insulin and may contribute to improved glycemic control, but the benefits must be balanced considering the side effects related to body weight gain and hypoglycemia. That review article recommended simple combination regimens such as insulin glargine plus metformin and/or a sulfonylurea. Such regimens are, however, largely different from the physiologic insulin secretion pattern.

Rapid-acting insulin secretagogues (glinides), which recently became available for clinical use, selectively enhance early post meal insulin secretion, resulting in improved postprandial glucose levels (7, 8) and rarely cause hypoglycemia. Delay in the early post meal insulin secretion is recognized as an early characteristic of type 2 diabetes and, therefore, the use of glinide is recommended. One previous study, however, showed that administration of mitiglinide three times a day in combination with insulin glargine plus metformin and/or a sulfonylurea. Such regimens are, however, largely different from the physiologic insulin secretion pattern.
Table 2. The Variables Measured in this Study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>12 weeks after glinide administration</th>
<th>12 weeks after glinide discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>125.7 ± 12.8</td>
<td>129.2 ± 14.4</td>
<td>130.0 ± 16.6</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>72.1 ± 10.1</td>
<td>73.9 ± 8.3</td>
<td>73.9 ± 10.8</td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td>207.1 ± 39.6</td>
<td>201.3 ± 37.9</td>
<td>201.1 ± 36.3</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>121.2 ± 30.8</td>
<td>115.2 ± 29.4</td>
<td>113.6 ± 31.8</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>139.9 ± 95.3</td>
<td>153.1 ± 114.8</td>
<td>141.9 ± 117.4</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>55.6 ± 15.0</td>
<td>54.2 ± 14.3</td>
<td>54.4 ± 14.4</td>
</tr>
<tr>
<td>BMI</td>
<td>24.1 ± 3.4</td>
<td>24.1 ± 3.5</td>
<td>24.0 ± 3.5</td>
</tr>
</tbody>
</table>

We showed a significant positive effect of glinide administration at lunchtime in combination with twice daily injections of premixed insulin. Although one might argue that the change in HbA1c levels of -0.2% after 12 weeks is a “tiny” difference, the difference in HbA1c levels between twice daily injections of premixed insulin and intensive insulin treatment over 26 weeks was also only 0.2% (7.0% vs 6.8%, respectively) in the PREFER study (10). Therefore, the results obtained in the present study are meaningful clinically. Serum 1,5-AG is recognized as a marker of postprandial hyperglycemia (11). Even though postprandial plasma glucose levels did not change in the present study, 1,5-AG levels tended to increase after the administration of glinide. This suggests that administration of glinide at lunchtime improved the postprandial state after lunch, leading to improvement of HbA1c in this study. In general, although intensive insulin therapy resembles the physiological insulin secretion pattern, type 2 diabetic patients, especially elderly patients, often complain of the difficulty or inconvenience of this treatment regimen. In this study, all 60 patients completed the study. Accordingly, the present results should be clinically relevant for many patients.

In conclusion, addition of glinide at lunchtime to twice daily injections of premixed insulin was shown to be an effective and safe option for treatment of type 2 diabetes. We propose that this kind of combination therapy be considered for type 2 diabetic patients to improve glycemic control and maintain compliance and adherence to treatment regimens.

References

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