NOTE

Long-term Effect of Combination Therapy with Mitiglinide and Once Daily Insulin Glargine in Patients who were Successfully Switched from Intensive Insulin Therapy in Short-term Study

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Abstract. We have previously reported the therapeutic efficacy of mitiglinide combined with once daily insulin glargine (mitiglinide regimen) after switching from multiple daily insulin regimen of aspart insulin and glargine (intensive insulin regimen) in inpatients with type 2 diabetes mellitus in two consecutive days. In the present study, we followed up 9 of the 15 responsive patients with these novel regimens for 6 months after discharge. The data collected from these patients were compared to those of 15 randomly chosen patients who had well matched background and received intensive insulin regimen during hospitalization which was continued after discharge. The average HbA1c level of these 9 patients with mitiglinide regimen at 6 months was 6.7 ± 0.8% and was comparable to that of the patients with intensive insulin regimen (HbA1c = 7.0 ± 1.0%). In conclusion, mitiglinide and insulin glargine combination therapy maintained fair glycemic control for as long as 6 months in subpopulation of Japanese patients with type 2 diabetes.

Key words: Type 2 diabetes, Postprandial hyperglycemia, Insulin analogue, Glinides

THE glinide, which include nateglinide, repaglinide, and mitiglinide, are novel, highly physiologic, meal-time glucose regulators recently approved for the treatment of type 2 diabetes. It has been previously reported that early-insulin secretion is disrupted in patients progressing from NGT to diabetes in Japanese population [1, 2]. Glinides selectively enhanced early meal-induced insulin secretion and thus improved postprandial hyperglycemia [3, 4] with few hypoglycemic episodes [5]. But in cases with advanced diabetes, in particular in those with persistently elevated fasting plasma glucose concentrations, many physicians select sulfonylurea as the next line antidiabetic agent, but these drugs do not effectively improve post-meal glycemic excursion. In this regard, the combined use of nateglinide or mitiglinide with insulin glargine, which has a 24-h time-action profile with no pronounced peak [6, 7], may be a potent regimen to lower postprandial hyperglycemia before switching to sulfonylurea or intensive insulin therapy using insulin injections.

We have previously reported that 30 inpatients with type 2 diabetes were switched to premeal mitiglinide combined with once daily insulin glargine after good glycemic control with the intensive insulin regimen (aspart t.d. plus once daily glargine) and fifteen of those patients showed similar daily profiles of blood glucose with mitiglinide and glargine regimen, as assessed by M value just after switching [8]. The clinical characteristics of the responders were of younger
age, heavier body weight, and required fewer dosage of bolus insulin per body weight kilogram [8]. We report here the long-term efficacy of combination therapy of mitiglinide with insulin glargine in the patients who showed short-term responsiveness to the combination therapy.

**Subjects and Methods**

Originally this study was planned prospectively and after providing informed consent, we randomly chose 30 hospitalized patients with type 2 diabetes mellitus who received intensive insulin therapy at the Juntendo University School of Medicine from June 2004 to March 2005 and were in good glycemic condition for at least two weeks or more. Selection and exclusion criterion and backgrounds of the patients are described in reference 8. After improvement of glycemic control with intensive insulin regimen, the regimen was switched to premeal administration of mitiglinide (20 mg for each meal) combined with once daily insulin glargine (at the same doses as the ones used in the intensive insulin regimen) (termed mitiglinide regimen). Background difference between 15 effectively or 15 ineffectively switched patients are described in reference 8. In summary, evaluation of short-term effectiveness was based on M values from 7 estimations of blood glucose, and the daily profiles of blood glucose were compared under each regimen on two consecutive days. Ten of 15 effectively switched patients were continued on mitiglinide regimen for 6 months. (One patient dropped out because of foot infection.) Five patients did not continue to receive the mitiglinide regimen due to transfer to other hospitals or inability of self-inject insulin after discharge. The data collected from these patients were compared to those of 15 randomly chosen patients who had well matched backgrounds (in particular BMI and body weight) and who received intensive insulin regimen during hospitalization, which was continued after discharge.

All data are expressed as mean ± SE. Differences between groups were examined for statistical significance using Student’s t-test. A P value less than 0.05 was regarded as statistically significant.

**Results**

We followed up 10 of the fifteen patients for 6 months. (One patient dropped out because of foot infection). Three patients transfered to other hospitals after discharge and two could not do the self-injection of insulin; these patients were switched to sulfonylurea therapy after discharge. The nine Japanese type 2 diabetic patients whose clinical backgrounds are shown in Table 1, had been well controlled glycemia with intensive insulin regimen in our hospital and were successfully switched to mitiglinide (20 mg before each meal) and glargine (in the same units as those with intensive regimen) regimen in short-term study. They continued to be treated with mitiglinide and glargine and 2 of 9 were able to discontinue glargine after several months because of improvement of fasting plasma glucose. The rest of these patients were able to successfully continue the same regimen for 6 months without increasing the amount of glargine. To evaluate the effectiveness of mitiglinide regimen, we compared it with that of intensive insulin regimen using premeal aspart insulin and basal glargine. The 15 independently chosen patients who had well matched backgrounds shown in Table 1 received intensive insulin regimen

Table 1. Comparison of clinical backgrounds between the patients with mitiglinide regimen or intensive regimen

<table>
<thead>
<tr>
<th></th>
<th>Mitiglinide regimen</th>
<th>Intensive regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>Male/female</td>
<td>4/5</td>
<td>11/4</td>
</tr>
<tr>
<td>Age</td>
<td>53.1 ± 5.5</td>
<td>57.3 ± 2.8</td>
</tr>
<tr>
<td>Body Weight (kg)</td>
<td>67.0 ± 6.4</td>
<td>65.6 ± 2.1</td>
</tr>
<tr>
<td>BMI</td>
<td>25.2 ± 1.3</td>
<td>24.7 ± 0.7</td>
</tr>
<tr>
<td>Duration of DM (years)</td>
<td>8.8 ± 1.9</td>
<td>6.4 ± 1.6</td>
</tr>
<tr>
<td>HbA1c</td>
<td>9.2 ± 0.8</td>
<td>9.7 ± 0.5</td>
</tr>
<tr>
<td>Daily dose of Aspart insulin (U/day)</td>
<td>16.4 ± 2.0</td>
<td>21.2 ± 1.4</td>
</tr>
<tr>
<td>Daily dose of Glargine (U/day)</td>
<td>10.4 ± 2.1</td>
<td>7.0 ± 0.9</td>
</tr>
<tr>
<td>Daily dose of Aspart per kgBW (U/day/kg)</td>
<td>0.26 ± 0.04</td>
<td>0.31 ± 0.02</td>
</tr>
<tr>
<td>Daily dose of Glargine per kgBW (U/day/kg)</td>
<td>0.15 ± 0.03</td>
<td>0.11 ± 0.01</td>
</tr>
<tr>
<td>History of SU treatment (yes/no)</td>
<td>4/5</td>
<td>7/8</td>
</tr>
<tr>
<td>History of insulin treatment (yes/no)</td>
<td>3/6</td>
<td>3/12</td>
</tr>
</tbody>
</table>

Data are mean ± SE or number. All data between mitiglinide regimen and intensive regimen showed no significant differences.
COMBINATION THERAPY WITH MITIGLINIDE AND GLARGINE

Fig. 1. Changes in HbA1c over 6 months (mean ± SE) in patients with mitiglinide + glargine regimen (closed circle) and those with intensive insulin regimen (open circle). Decreases of HbA1c at all points (2–6 months) in both regimens were statistically significant from HbA1c at baseline (month 0) (p<0.01). The difference between the two regimens at each point was not significant.

during hospitalization, which was continued after discharge.

As shown in Fig. 1, the mean glycosylated hemoglobin levels of the nine patients with mitiglinide regimen were originally 9.2 ± 2.4%, 7.2 ± 1.0% at 2 months after switching, 6.7 ± 0.8% at 4 months after switching, and 6.6 ± 0.8% at 6 months after switching, resulting in significant improvement of glycemic control. Mean plasma fasting glucose levels were originally 123.0 ± 4.7 mg/dl and 124.4 ± 5.5 mg/dl after 6 months. Hypoglycemic symptoms were not observed nor was their mean body weight changed for the period in either the intensive regimen or mitiglinide regimen group. The effectiveness was comparable to that of the 15 patients who started intensive insulin regimen during hospitalization and continued after discharge (HbA1c were originally 9.7 ± 2.2%, 7.4 ± 1.1% at 2 months after switching, 6.8 ± 1.0% at 4 months after switching, and 7.0 ± 1.0% at 6 months after switching) (Fig. 1).

To confirm that mitiginide actually contributes to this regimen, we interrupted mitiglinide for 1 day (only 3 times) to check self-monitoring blood glucose data, and compared the blood glucose daily profiles between those with mitiglinide and those without it. The profiles of these patients were obviously worse on the day without mitiglinide in all patients (data not shown). These results indicated that mitiglinide contributes to this regimen even after 6 months from start of this regimen.

Discussion

It has been previously reported that mitiglinide selectively enhanced early meal-induced insulin secretion and thus improved postprandial hyperglycemia [9] as well as nateglinide did [2, 3]. Therefore the glycemic control of those cases whose fasting or premeal glucose level is considerably high, may not be able to be improved effectively. For this reason metformin, which lowers fasting plasma glucose, has been recommended as a supplement to nateglinide therapy [10, 11]. But combination therapy using glargine as a basal insulin with a glinide has not been reported previously.

As a combination therapy using oral hypoglycemic agent with basal insulin, once daily glargine with sulfonylurea plus metformin has been reported by Janka et al. as safer and more effective than beginning twice-daily injections of 70/30 premixed insulin and discontinuing oral antidiabetic drugs [12]. Combination therapy using glargine and rapid acting insulin is presently the most powerful regimen, but from our study, mitiglinide regimen was comparable to that of the patients with intensive insulin regimen once the effectiveness of mitiglinide was confirmed by short-term (one day) treatment. As previously described in our short-term study, the characteristics of the responders with short-term treatment with mitiglinide regimen were of younger age and heavier body mass index and body weight. But baseline treatment before starting intensive insulin regimen including insulin and sulfonylurea, did not show any difference between effective and ineffective groups. The insulin doses, including aspart insulin, glargine, and total insulin, were not different between the two groups. Only insulin doses of aspart per body weight kilogram were significantly fewer in the effective group than in the ineffective group.

In comparison with intensive regimen, mitiglinide regimen may be expected to be beneficial to these patients in terms of convenience, pain relief, compliance of drugs, and patient satisfaction. In conclusion, mitiglinide may be a potent candidate for the treatment partner with basal insulin replacement with glargine in subpopulation of Japanese type 2 diabetes.

Appendix: This study named as JUN-LAN Study was supported by associated hospitals of Juntendo University.
References


