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Efficacy of conversion from bedtime NPH insulin to morning insulin glargine in type 2 diabetic patients on basal-prandial insulin therapy

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Abstract

In normal subjects, approximately half of the daily insulin requirement constitutes basal insulin. We investigated whether increasing the dose of insulin glargine up to half of the total insulin requirement could lead to better glycemic control in type 2 diabetic patients who were treated on basal-prandial insulin therapy. A total of 62 patients with type 2 diabetes on mealtime rapid-acting insulin analogue and bedtime NPH were randomized to either continuation of bedtime NPH ($n = 31$) or morning glargine ($n = 31$) for 6 months while continuing the aspart/lispro at each meal. The two groups were matched for age, sex, diabetes duration, BMI, HbA_{1C}, endogenous insulin secretion, and proportion of numbers using aspart/lispro and using oral hypoglycemic agents. The dose of insulin glargine was increased by 2–4 units to meet the target fasting blood glucose, whereas the dose of NPH was principally unchanged as a control group. Mean HbA_{1C} at baseline was similar between patients with glargine and NPH (7.2% versus 6.9%). The percentage of glargine dose increased significantly (31% at baseline to 48% at 6 months) without any significant changes in total insulin dose. Mean HbA_{1C} at 3 months was 6.6% with glargine and 7.0% with NPH ($P < 0.0001$, adjusted mean change between-treatment difference 0.6% [95% CI 0.3–0.9]), and the values at 6 months were 6.6% and 6.9%, respectively ($P = 0.007$). Frequency of hypoglycemia did not differ between the groups. Increasing the dose of glargine without changing the total daily insulin dose resulted in significantly better glycemic control in type 2 diabetic patients on basal-prandial insulin therapy. Conversion from bedtime NPH to morning glargine appears efficacious with no increase in frequency of hypoglycemia.

Keywords: Glargine; Intensive insulin therapy; Type 2 diabetes; Basal-prandial insulin therapy

1. Introduction

Newer insulin therapies, including the concept of physiologic basal-prandial insulin and the availability of insulin analogues, are changing clinical diabetes care [1]. Physiologic basal-prandial insulin therapy may achieve lower HbA_{1C} levels without additional hypoglycemia. Aiming at normal blood glucose control can contribute to delaying the onset and progression of the microvascular complications, and possibly of the macrovascular complications, within the range of favorable cost-effectiveness not only in type 1 but also in type 2 diabetes [2–4].

A new insulin analogue, glargine, has been developed [5]. It is a long-acting insulin with a more favorable 24-h time-action profile with no pronounced peak than conventional long- or intermediate-acting

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insulin (i.e., NPH insulin). It can mimic the physiological basal insulin profile. In normal subjects and often in diabetic patients undergoing continuous subcutaneous insulin infusion (CSII), approximately half of the daily insulin requirement constitutes basal insulin [6–10]. However, in most of the studies using multiple daily injection with mealtime regular insulin and bedtime NPH insulin, NPH insulin was used within 20–40% of total daily dose, since increasing the dose of bedtime NPH insulin is often accompanied with a fear of nocturnal hypoglycemia [10–13]. Insulin glargine may cause less hypoglycemia with respect to basal insulin replacement [11,12,14,15]. The above background and the following facts together may suggest that bedtime NPH insulin can be shifted to morning insulin glargine: (1) glargine appears to last nearly 24 h [5], (2) morning insulin glargine has been reported to provide better glycemic control than bedtime insulin glargine or bedtime NPH insulin both in type 1 [16] and type 2 diabetes [17], and (3) morning glargine would be easier for patients than bedtime glargine with respect to the adherence to insulin therapy.

In this study we hypothesized that increasing the dose of morning glargine up to half of the total insulin requirement may lead to better glycemic control. To test the hypothesis we investigated type 2 diabetic patients who were treated on basal-prandial insulin therapy, i.e., mealtime rapid-acting insulin analogue and bedtime NPH insulin, and shifted from bedtime NPH insulin to morning insulin glargine to clarify the effect.

2. Patients and methods

2.1. Subjects

Subjects had type 2 diabetes of at least 2 years' known duration, were aged at least 35 years, and had negative tests for anti-GAD antibody (GADAb Cosmic, Tokyo, Japan) without any episodes of ketoacidosis, BMI $\leq$ 40 kg/m^2, and HbA_{1C} level $\leq$ 10%. They once had poor glycemic control (HbA_{1C} level $\geq$ 8%) despite optimal dose of sulfonylureas in addition to diet and exercise therapy, and for more than 1 year they were on basal-prandial insulin therapy using aspart/lispro at each meal and NPH at bedtime by pen administration with or without anti-diabetic oral agents. Subjects with impaired hepatic, renal, or cardiac function or recurrent major hypoglycemia were excluded. A total of 62 patients participated in the study. All patients were treated intensively with basal-prandial insulin therapy, and achieved stable glycemic control. Patients were requested to measure capillary blood glucose before meals, 1.5–3 h after meals and at bedtime every week. It was suggested that they: (1) decrease or increase the dose of basal insulin if fasting blood glucose was repeatedly <6.0 or >7.8 mmol/l (<108, >140 mg/dl), (2) decrease or increase the dose of rapid-acting insulin at meals if the post-prandial blood glucose was repeatedly <7.0 or 9.5 mmol/l (<126, >171 mg/dl), and (3) adjust the dose of rapid-acting insulin on the basis of post-prandial blood glucose of previous days and episode of hypoglycemia, as well as the composition and size of meals and physical activity. However, achieving the above goal was not easy due to a fear of hypoglycemia, insulin-resistance/obesity, and maybe insufficient life-style intervention.

The study was carried out in accordance with the Helsinki Declaration II and was approved by the local ethic study committee. After a 3-month run-in period during which previous insulin treatment was continued, the patients were randomized to either continuation of NPH at bedtime ($n = 31$) or once daily glargine at breakfast ($n = 31$) for 6 months while continuing the aspart/lispro at each meal. The two groups were matched for age, sex, diabetes duration, BMI, HbA_{1C}, endogenous insulin secretion level evaluated by urinary C-peptide excretion [13], and proportion of numbers using aspart/lispro and using oral hypoglycemic agents (P = NS between groups).

The dose of insulin glargine was increased by 2–4 units, if necessary, to meet the target fasting blood glucose whereas the dose of NPH was principally left unchanged as a control group. When the dose of insulin glargine was increased, mealtime rapid-acting insulin analogue was recommended to be reduced by 1–2 units in order to avoid post-prandial hypoglycemia due to improvement in the pre-prandial glucose levels. The total daily dose of insulin was principally unchanged. All patients in both groups were seen every month in the outpatient clinic. Hypoglycemia was defined as any episode in which clinical symptoms were confirmed or blood glucose level was confirmed <3.3 mmol/l (60 mg/dl). Hypoglycemia was considered mild when the episodes were self-treated by the patients and severe when the episode required any kind of external help.

2.2. Methods

Capillary whole blood glucose was measured by the Glutest (Sanwa Kagaku, Nagoya, Japan). The HbA_{1C} level was measured by HPLC (ADAMS^{TM} A_{1C} HA8160, Arkray, Kyoto, Japan, normal range, 4.3–5.8%). The method was standardized by the Japan Diabetes Society, aligned with the one used in the