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RAPID COMMUNICATION

The Effects of Nateglinide Following Oral Glucose Load in Impaired Glucose Tolerance Subjects: Rapid Insulin Stimulation by Nateglinide in IGT Subjects

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Abstract. This study was designed to determine the effect of a novel insulin secretagogue, nateglinide, on the glycemic response curve and early insulin secretion following oral glucose load in impaired glucose tolerance (IGT) subjects. Thirteen subjects were given a 75 g oral glucose tolerance test (75 g OGTT), the findings of which resulted in the diagnosis of IGT. The subjects returned to our hospital immediately. Eight subjects, in whom neither body weight nor life style (daily diet and exercise) was significantly altered during this period, were given 90 mg of nateglinide 5 min before a second oral glucose load in order to examine restoration of impaired early insulin secretion. Nateglinide administration resulted in the almost normalization of the glycemic response curve with restoration of impairment in early insulin response at 30 and 60 min after an oral glucose load. The area under the secreted insulin-time curve was not changed significantly by nateglinide administration. A single dose of nateglinide was shown to almost normalize the glycemic response curve after a 75 g OGTT and to restore impairment in early insulin response in IGT subjects.

Key words: Impaired glucose tolerance, Early prandial insulin secretion, Nateglinide, Type 2 diabetes

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THE incidence of type 2 diabetes has increased dramatically over the past 10 years, largely due to changes in life style and an increasing prevalence of obesity [1]. The earliest determinant of progression to type 2 diabetes is a loss of early insulin secretion, a defect which results in postprandial hyperglycemia and is often believed to reflect insulin resistance [2]. This development first manifests itself as impaired glucose tolerance, which may then progress to type 2 diabetes [2, 3]. Therefore, an insulin secretagogue, which selectively enhances early meal-induced insulin secretion and thus improves postprandial hyperglycemia, could provide a valuable treatment option in the prevention of type 2 diabetes.

Nateglinide is a novel highly physiologic, mealtime glucose regulator recently approved for the treatment of type 2 diabetes [4–8]. When compared to sulfonylurea therapy, nateglinide selectively enhanced early meal-induced insulin secretion and thus improved mealtime glucose control, possibly decreasing overall insulin exposure [9]. In order to assess whether nateglinide induces improvement in the glycemic response curve and in the loss of early insulin secretion without increasing total insulin exposure in IGT subjects, a 75 g oral glucose tolerance test (OGTT) was performed twice, once with and once without administration of nateglinide prior to the oral glucose load.

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Subjects and Methods

Subjects

Thirteen impaired glucose tolerance (IGT) subjects newly diagnosed at our hospital according to American Diabetes Association's criteria (1997), were provided informed consent. The body mass index of each subject was more than 25.0 kg/m^2.

Experimental design

The subjects were given a 75 g OGTT. Eight of these subjects were given a second 75 g OGTT within a month. On the second occasion, subjects were administered 90 mg of nateglinide 5 min before the oral glucose load. Five of the original 13 subjects were excluded from the second OGTT since they demonstrated significant changes in body weight and/or life style (diet and exercise) in the period since the first OGTT. Blood samples from the remaining 8 subjects (4 male and 4 female, age (mean ± SD) 54.5 ± 8.2 years, body mass index (mean ± SD) 27.3 ± 3.0) were taken for determination of serum glucose and immunoreactive insulin concentrations before glucose load and at 30, 60, 120 and 180 min after glucose load, respectively. Mean homeostasis model insulin resistance index (HOMA-R) following the first OGTT was (mean ± SD) 2.6 ± 1.1, while that following the second was 2.4 ± 1.1 (there was no significant difference between the first and second HOMA-R values; $p = 0.55$). Paired t-testing was used to compare the results from the first and second 75 g OGTT. P values<0.05 were considered to be statistically significant.

Results

Serum glucose levels were observed to be significantly decreased 60 min after oral glucose load following nateglinide administration (164.0 ± 28.1 mg /dl compared to the control value of 210.5 ± 28.5 mg /dl; $p = 0.0017$). At 120 min after glucose load, serum glucose levels of 7 subjects decreased to less than 140 mg/dl (123.3 ± 22.7 mg/dl compared to the control value of 170.6 ± 16.7 mg/dl; $p = 0.00077$). Average area under the serum glucose-time curve also was decreased significantly (23.8 ± 3.3 g min/dl compared to the control value of 29.4 ± 2.9 g min/dl; $p = 0.0013$), as shown in Fig. 1A.

There was no significant difference in mean total area under the serum insulin-time curve (AUC-IRI) following nateglidine administration (11.5 ± 4.4 U min/l compared to the control value of 11.2 ± 4.0 U min/l; $p = 0.71$). Following nateglidine administration, serum insulin concentrations were significantly higher at 30 and 60 min after oral glucose load (30 min: nateglidine 74.7 ± 34.6 μU/ml, control 34.7 ± 20.7 μU/ml, $p = 0.0034$; 60 min: nateglinide 87.1 ± 39.6 μU/ml, control 67.5 ± 32.0 μU/ml, $p = 0.029$) but significantly lower at 120 min after oral glucose load (nateglinide 66.4 ± 22.6 μU/ml, control 96.0 ± 28.9 μU/ml, $p = 0.0070$) as shown in Fig. 1B.

Compared to control readings, AUC-IRI value was significantly higher during 0–60 min after oral glucose load (nateglinide 3.7 ± 1.5 U min/l, control 2.2 ± 1.1 U min/l; $p = 0.0016$) and significantly lower during 120–180 min after oral glucose load (nateglinide 3.2 ± 1.2 U min/l, control 4.1 ± 1.4 U min/l; $p = 0.036$) following nateglidine administration. No subject demonstrated any hypoglycemic symptom after nateglinide administration.

Discussion

Recently, there have been reports that fasting glucose concentrations alone do not identify individuals at increased risk of death associated with hyperglycemia and that meal time glycemia contributes significantly to overall glycemic control and coronary artery disease mortality [10–12]. In this regard, IGT subjects already have a great attributable risk of death as do type 2 diabetes patients. Nateglinide selectively enhances early meal-induced insulin secretion and thus improves mealtime glucose control. Consistent with the more physiological nature of nateglinide, overall insulin exposure is relatively lower than that produced by sulfonylurea medication in type 2 diabetes [9]. In the present study, we have shown that nateglinide administration results in improvement of the impairment in early insulin secretion and of the serum glucose response curve after oral glucose load in IGT subjects. There was no significant difference in mean total area under the insulin-time curve (AUC-IRI). Nateglinide administration resulted in a more enhanced physiological

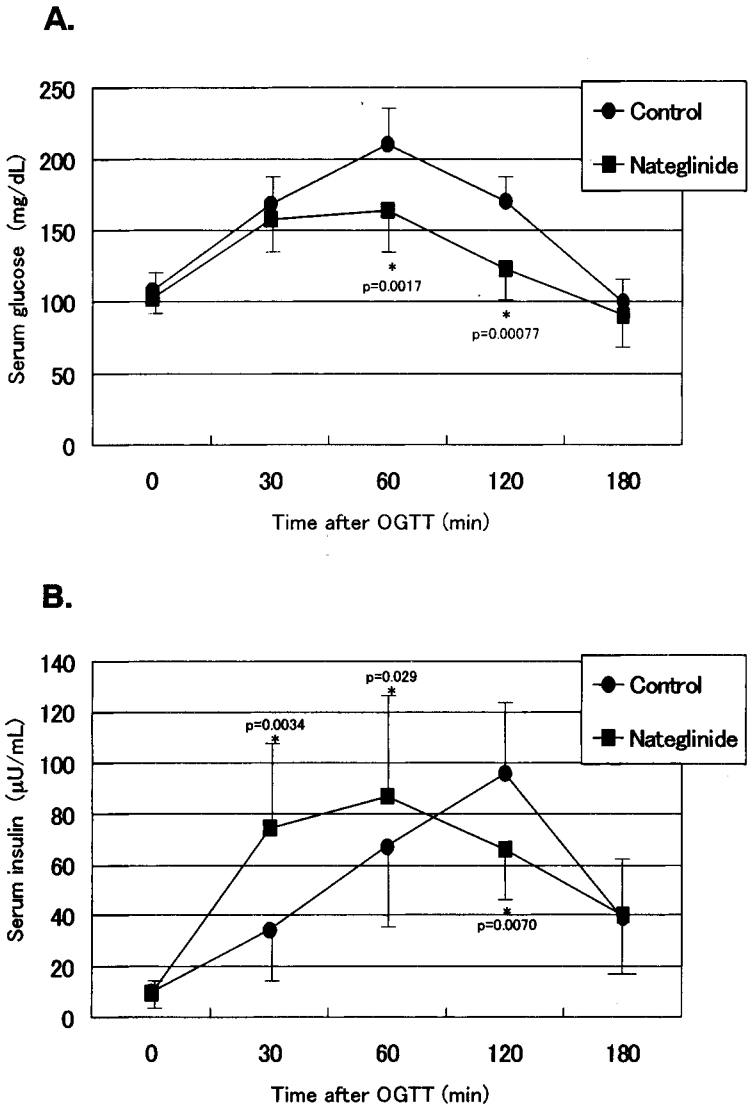

Fig. 1. A. Glycemic responses during a 75 g OGTT, with or without nateglinide (90 mg p.o.) pre-administration, in IGT subjects. Asterisks denote a significant difference compared to the without nateglinide administration values. B. Serum insulin concentrations during a 75 g OGTT, with or without nateglinide (90 mg p.o.) pre-administration, in IGT subjects. Asterisks denote a significant difference compared to without nateglinide administration values. Data are shown as mean ± SD.

pattern of insulin secretion without increasing the total amount of secreted insulin. These effects reduced the occurrence of glucose extremes as well as reactive hyperinsulinemia (AUC-IRI 120–180 min). Uchino *et al.* recently reported in Japanese obese type 2 diabetes patients that nateglinide improved impairment in early insulin response and resulted in an almost normalization of the glucose response curve after glucose load without increasing overall insulin exposure [13]. In healthy subjects nateglinide has been shown to provide a rapid and shorter-lived stimulation of insulin secretion, resulting in lower meal-related glucose elevation [14]. This is the first report indicating that nateglinide improves the glycemic curve and the pattern of insulin secretion in IGT. Because a normal pattern of insulin secretion is essential for the effective control of postprandial hyperglycemia and, even though a post glucose load condition is clearly distinct from a postprandial one, the possibility exists that nateglinide may prevent the

progression from IGT to type 2 diabetes. The capability of nateglinide and repaglinide which are targeted to preserve beta-cell function and to delay or prevent functional beta-cell loss has been reported in animal models [15, 16]. Recently, a nateglinide and valsartan in Impaired Glucose Tolerance Outcome Research (Navigator) study was launched as the largest diabetes prevention trial [17]. One purpose of this clinical study is to determine whether nateglinide has preventive effect on progression from IGT to type 2 diabetes.

Conclusion

A single dose of nateglinide was shown to almost normalize the glycemic response curve after a 75 g OGTT and to restore impairment in early insulin response in IGT subjects.

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