Efficacy and Safety of Once Daily Gliclazide (20 mg/day) Compared with Nateglinide

SHINNYA MIWA, HIROTAKA WATADA, CHIE OHMURA, YASUSHI TANAKA AND RYUZO KAWAMORI

Department of Medicine, Metabolism and Endocrinology, Juntendo University, School of Medicine, Tokyo 113-8421, Japan

Abstract. An open-label prospective cross-over trial was performed to compare the efficacy and safety of once daily low-dose gliclazide (20 mg/day) with that of nateglinide at the usual dosage (270 mg/day, 90 mg t.i.d.) in Japanese type 2 diabetics with relatively good glycemic control ($HbA_{1c} < 7.0\%$). Eight patients received 20 mg/day of gliclazide and 16 received 270 mg/day of nateglinide. After at least 12 weeks of gliclazide or nateglinide therapy, the drugs were switched and treatment was continued for another 12 weeks. The final HbA_{1c} value was modestly, but significantly, lower after gliclazide treatment than after nateglinide treatment (6.2% vs. 6.4%). However, symptoms related to hypoglycemia were significantly more common with gliclazide treatment than nateglinide treatment (7 vs. 0 cases), although there were no severe hypoglycemic events. While gliclazide acts as a free radical scavenger, there was no effect on parameters of oxidative stress such as malondialdehyde-modified low density lipoprotein and thiobarbituric acid-reactive substances at the low dosage tested. In conclusion, both drugs are reasonable options for early type 2 diabetes. Compared with the regular dose of nateglinide, 20 mg/day of gliclazide achieved modestly better glycemic control with an increased frequency of hypoglycemia in diabetic patients with relatively good glycemic control.

Key words: Early type 2 diabetes, Postprandial hyperglycemia, Oral antidiabetic drug

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THE main goal of antidiabetic therapy is to prevent the complications of diabetes. Recent studies have demonstrated that the postchallenge and postprandial hyperglycemic peaks may be prospective determinants of vascular damage in early type 2 diabetes and even in persons with impaired glucose tolerance [1–3]. These findings imply that we should treat patients with early type 2 diabetes more aggressively and therefore should continue to search for more effective and safer antidiabetic drugs for early diabetes.

Nateglinide is a D-phenylalanine derivative that is an insulinotropic agent with a rapid onset and short duration of action [4–6]. It is used as a mealtime insulin secretagogue in the treatment of type 2 diabetes.

By reducing the postprandial blood glucose peak, nateglinide lowers the 24-h blood glucose profile and reduces the HbA_{1c} level. Based on its mechanism of reducing the blood glucose level, nateglinide therapy is believed to be associated with a low risk of hypoglycemia. In Japan, administration of 90 mg of nateglinide before each meal is the most common dosage. While it seems to be excellent for reducing postprandial hyperglycemia, taking the drug three times a day is inconvenient for some patients and might be an obstacle to compliance with therapy. In addition, the cost of nateglinide is higher than that of sulfonylurea agents which are also frequently used insulin secretagogues. For example, 20 mg of gliclazide costs 16 yen in Japan, while 270 mg of nateglinide costs 186 yen.

Sulfonylurea agents stimulate basal insulin secretion and also augment glucose-induced insulin release more markedly [7]. Gliclazide, a second-generation sulfonylurea, is one of the agents prescribed frequently in Japan since it is associated with a low risk of hypoglycemia [8]. Some clinical studies and clamp

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Correspondence to: Dr. Hirotaka WATADA, Department of Medicine, Metabolism and Endocrinology, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan

experiments in type 2 diabetic patients have demonstrated that gliclazide induces substantial first-phase insulin release [9, 10], hence this drug is potentially useful for reducing postprandial hyperglycemia. Besides its effect on hyperglycemia, gliclazide has been shown to possess antioxidant properties, such as inhibition of oxidation of low density lipoprotein (LDL) and reduction of platelet reactivity [11, 12]. It appears that these antioxidant effects of gliclazide are independent of any influence on glycemic control.

Compared with 270 mg/day of nateglinide (90 mg t.i.d.), a dose of 40 mg of gliclazide (recommended as the minimum dose for treatment of diabetes in Japan) is more effective for reducing the blood glucose level and HbA_{1c} levels in patients with type 2 diabetes. Therefore, if used in early type 2 diabetics, the frequent occurrence of hypoglycemic events could be anticipated. On the other hand, half the usual dose of gliclazide (20 mg once daily) might be convenient and effective for patients with early type 2 diabetes, but there have been only a few studies of its efficacy and safety in Japan.

Accordingly, to evaluate the efficacy and safety of 20 mg/day of gliclazide, we compared it with the regular dose of nateglinide (270 mg/day). The primary effect of each treatment was evaluated by monitoring the levels of HbA_{1c}, glycated albumin (Gly-Alb), and 1,5-anhydroglucitol (1,5-AG). To assess whether this low dose of gliclazide still had an antioxidant effect, the parameters of the oxidative status were evaluated, such as malondialdehyde-modified LDL (MDA-LDL) and thiobarbituric acid-reactive substances (TBARS). Body weight changes and the frequency of hypoglycemic events were also assessed as markers of safety.

Materials and Methods

Subjects

Patients eligible for enrollment were adults (≥ 20 years old) who had suffered from type 2 diabetes diagnosed according to World Health Organization criteria for at least 1 year. We excluded patients with renal failure (a serum creatinine level of more than 1.5 mg/dl) and patients with anemia (Hb < 12 g/dl) or other severe diseases, such as liver cirrhosis. At the time of enrollment in the study, patients were taking either 270 mg/day of nateglinide (90 mg before each meal) ($n = 16$)

or 20 mg of gliclazide once in the morning ($n = 8$). They had been treated for more than 12 weeks and showed stable (variation by less than 0.5% over 12 weeks) levels of HbA_{1c} with relatively good glycaemic control (HbA_{1c} less than 7.0%). In each patient, other parameters did not show remarkable changes over 12 weeks. Patients taking α -glycosidase inhibitors (acarbose or voglibose) and/or biguanides (metformin) as additional anti-diabetic drugs could be enrolled, provided that the dose was not changed during this study. Patients taking other anti-diabetic agents were excluded. None of the patients were taking antioxidants such as vitamin C, vitamin E, or probucol. The total number of patients enrolled was 24 (17 men and 7 women). All of the subjects gave informed consent to participation in this open-label prospective cross-over study and it was approved by the Ethical Committee of Juntendo University.

Study protocol

Subjects already being treated with nateglinide or gliclazide continued to take the respective drug for 3 months. Then a fasting blood sample was collected from each patient. Subsequently, the subjects on nateglinide switched to gliclazide and the subjects on gliclazide switched to nateglinide for 3 months, after which another fasting blood sample was collected. Each patient was reviewed once a month with the general health, compliance with medication, body weight, and frequency of hypoglycemia-related symptoms being checked at each visit (Fig. 1).

Assays

Blood was collected from each subject and HbA_{1c}, Gly-Alb, 1,5-AG, glucose, immunoreactive insulin (IRI), vitamin E, β -carotene, TBARS, MDA-LDL, total cholesterol, high density lipoprotein (HDL)-cholesterol, LDL-cholesterol, and triglycerides were measured by SRL Co. (Tachikawa, Japan). To measure TBARS, a test kit (Wako, Osaka, Japan) was used according to the method described previously [13]. To measure MDA-LDL, an ELISA method was used that was based on the principle previously reported by Kotani *et al.* [14]. To estimate the extent of cholesterol peroxidation, the level of 3,5,7-cholestatriene (3,5,7-Tri) in erythrocyte membranes was measured using gas chromatography-mass spectrometry, as de-

Fig. 1. Study Protocol

The study protocol is shown in this scheme. Blood samples were obtained in 0 week from both groups and were used to measure baseline data (A and B). Blood samples obtained in week 0 (nateglinide-to-gliclazide group) or week 12 (gliclazide-to-nateglinide group) were used for evaluation of the effect of nateglinide (B and C). Blood samples obtained in week 0 (gliclazide-to-nateglinide group) and week 12 (nateglinide-to-gliclazide group) were used for evaluation of the effect of gliclazide (A and D).

scribed previously [15].

Data analysis

Laboratory data were compared between the groups using Student's paired t-test, and Fisher's test was used for the frequency of hypoglycemia-related symptoms. All laboratory results are expressed as mean $\pm$ SD.

Results

The demographic characteristics and baseline data of the patients are summarized in Table 1. There are no differences in the data shown in Table 1 between the two groups. Five patients did not complete this study. Among them, four did not return for follow-up. The other patient was unable to continue gliclazide therapy because frequent (but not severe) hypoglycemic events occurred after switching from nateglinide to gliclazide. Therefore, we evaluated the efficacy of gliclazide in 19 subjects. All the subjects took their drug almost exactly as specified.

The laboratory data obtained before and after switching drugs in each group are shown in Table 2. Baseline HbA_{1c} was higher, and baseline 1,5AG, IRI and TBA were lower in nateglinide- to -gliclazide

group. The parameters used for evaluation of each drug are summarized in Table 3. The primary parameters of efficacy measured were HbA_{1c} and glycated albumin. Comparison of the two drugs showed that gliclazide caused a greater decrease of blood glucose than nateglinide (HbA_{1c}, $6.2 \pm 0.5\%$ vs. $6.4 \pm 0.4\%$; Gly-Alb, $19.2 \pm 3.2\%$ vs. $20.0 \pm 3.6\%$). In relatively well-controlled patients such as those recruited for this study, 1,5-AG is known to reflect postprandial hyperglycemia [16]. Although there was no significant difference of 1,5-AG levels between the two groups, the mean value was higher during gliclazide treatment than during nateglinide treatment.

FPG and fasting IRI values showed no differences between the two groups. These results suggested that a 20-mg morning dose of gliclazide did not enhance basal insulin secretion at 24 hours after administration.

One of the major concerns with sulfonylurea agents is hypoglycemic events. In this study, patients were asked to report hypoglycemic symptoms at baseline and at each follow-up visit. At baseline, only one patient taking gliclazide had hypoglycemic symptoms. However, among the 16 patients who switched from nateglinide to gliclazide, 6 patients started to experience new hypoglycemic events, such as apprehension, nervousness, tremor, and palpitation. In all cases, the symptoms were mild and improved soon after eating a snack. The baseline HbA_{1c} level of the patients with

Table 1. Clinical characteristics of the patients

	Gliclazide-to-Nateglinide Group	Nateglinide-to-Gliclazide Group	Total
N	8	16	24
Age (years)	64.0 ± 9.2	61.5 ± 7.3	62.3 ± 7.8
Male/Female	7/1	10/6	17/7
BMI (kg/m ²)	23.2 ± 2.4	22.4 ± 2.4	22.6 ± 2.3
Duration of diabetes (years)	11.2 ± 7.5	7.6 ± 5.9	8.6 ± 6.4
Other antidiabetic medicine			
Voglibose	1	3	4
Metformin	1	2	3
Completion status			
Completed	4	15	19
Did not complete 6 months	4	1	5

Data are expressed as n or mean ± SD.

Table 2. Laboratory data and the number of patients with hypoglycemic symptom in each group before and after switching drugs

	Gliclazide-to-Nateglinide Group		Nateglinide-to-Gliclazide Group	
	0 week	12 weeks	0 week	12 weeks
BMI (kg/m ²)	23.7 ± 2.1	23.7 ± 2.1	22.3 ± 2.5	22.4 ± 2.4
Systolic BP (mmHg)	123.0 ± 10.1	126.8 ± 11.2	128.1 ± 18.3	123.7 ± 17.9
Diastolic BP (mmHg)	66.0 ± 4.9	70.5 ± 9.5	72.5 ± 10.7	74.7 ± 11.4
HbA _{1c} (%)	5.8 ± 0.5	6.2 ± 0.6	6.5 ± 0.4*	6.3 ± 0.4
Gly-Alb (%)	17.9 ± 3.0	17.8 ± 2.5	20.6 ± 3.7	19.6 ± 3.2†
1,5-AG (μg/ml)	17.3 ± 5.6	12.0 ± 5.4	8.0 ± 6.4*	8.1 ± 5.5
FBS (mg/ml)	126.0 ± 18.0	133.8 ± 7.8	128.0 ± 16.3	131.7 ± 17.0
IRI (μg/ml)	12.2 ± 3.8	10.3 ± 1.4	5.7 ± 3.9*	5.5 ± 3.6
Vitamin E (mg/dl)	1.3 ± 0.2	1.2 ± 0.4	1.5 ± 0.4	1.3 ± 0.4
β-carotene (μg/dl)	46.5 ± 16.0	45.7 ± 20.8	59.9 ± 54.0	53.9 ± 47.0
3,5,7-cholestatriene (%)	1.1 ± 0.1	1.0 ± 0.2	1.1 ± 0.3	1.1 ± 0.5
TBA (nmol/ml)	4.4 ± 2.3	4.7 ± 2.4	2.8 ± 0.8*	3.0 ± 0.8
MDA-LDL (U/l)	101.0 ± 28.2	87.6 ± 21.2	106.5 ± 38.3	111.8 ± 36.8
T-cho (mg/dl)	188.3 ± 20.9	191.5 ± 39.5	217.5 ± 27.7	208.9 ± 29.4
HDL (mg/dl)	47.8 ± 11.1	45.8 ± 5.1	62.9 ± 21.8	62.9 ± 20.8
LDL (mg/dl)	118.8 ± 25.9	119.8 ± 39.7	127.1 ± 29.9	119.8 ± 22.0
TG (mg/dl)	135.5 ± 46.7	120.3 ± 67.2	112.7 ± 62.8	111.0 ± 56.7
Frequency of hypoglycemia	1	0	0	6†

Data are expressed as the mean ± SD or n. Student's paired t-test was used to compare laboratory data between the groups and Fisher's test was used to compare the number of patients with hypoglycemic symptom between the two groups. *p<0.05 vs baseline data of gliclazide-to-nateglinide group. †p<0.05 vs baseline data of nateglinide-to-gliclazide group.

hypoglycemic events did not differ from that of the other 10 patients (6.4 ± 0.3% in patients with hypoglycemia after taking gliclazide vs. 6.5 ± 0.4% in patients without hypoglycemia). Thus, we could not predict the occurrence of hypoglycemic events from the baseline HbA_{1c} level. On the other hand, none of the 8 patients who changed from gliclazide to nateglinide developed new hypoglycemia-related events and the existing hypoglycemic symptoms of one patient disappeared after the change to nateglinide.

Thus, the frequency of hypoglycemic events was significantly higher during gliclazide therapy than during nateglinide therapy (7 cases vs. 0 cases, p<0.01) (Table 3).

Another concern with sulfonylurea agents is weight gain, but significant change of BMI was not observed in either stage of the study (Table 3).

Gliclazide was anticipated to have an antioxidant effect, but the levels of antioxidant vitamins (vitamin E and β-carotene) and parameters that reflect oxidative

Table 3. Comparison of the effects of gliclazide and nateglinide

	Gliclazide	Nateglinide	P value
BMI (kg/m ²)	22.6 ± 2.3	22.5 ± 2.4	n.s.
Systolic blood pressure (mmHg)	123.5 ± 16.3	127.8 ± 16.8	n.s.
Diastolic blood pressure (mmHg)	72.8 ± 10.9	72.1 ± 10.3	n.s.
HbA _{1c} (%)	6.2 ± 0.5	6.4 ± 0.4	<0.05
Gly-Alb (%)	19.2 ± 3.2	20.0 ± 3.6	<0.05
1,5-AG (μg/ml)	10.0 ± 6.6	8.8 ± 6.3	n.s.
FBS (mg/ml)	130.5 ± 16.8	129.2 ± 15.0	n.s.
IRI (μg/ml)	6.9 ± 4.5	6.6 ± 4.0	n.s.
Vitamin E (mg/dl)	1.3 ± 0.4	1.4 ± 0.4	n.s.
β-carotene (μg/dl)	52.3 ± 42.1	56.9 ± 48.7	n.s.
3,5,7-cholestatriene (%)	1.1 ± 0.5	1.1 ± 0.3	n.s.
TBA (nmol/ml)	3.3 ± 1.3	3.2 ± 1.5	n.s.
MDA-LDL (U/l)	109.5 ± 34.8	102.5 ± 35.8	n.s.
T-cho (mg/dl)	204.6 ± 28.6	221.1 ± 31.3	n.s.
HDL (mg/dl)	59.7 ± 19.9	59.3 ± 20.6	n.s.
LDL (mg/dl)	119.6 ± 22.1	125.5 ± 31.1	n.s.
TG (mg/dl)	116.2 ± 54.5	114.3 ± 61.9	n.s.
Frequency of hypoglycemia	7	0	<0.01

Data are expressed as the mean ± SD or n. Student's paired t-test was used to compare laboratory data between the groups and Fisher's test was used to compare the number of patients with hypoglycemic symptoms between the two groups.

stress (TBA, MDA-LDL, and 3,5,7-Tri) did not differ between the two groups (Table 3).

Discussion

In Japan, 20 mg/day of gliclazide is frequently used to treat early type 2 diabetes, despite the lack of any data to prove its efficacy and safety. As a first step to elucidating the efficacy of this dose of gliclazide in patients with early type 2 diabetes, we recruited patients who were already treated with either 20 mg/day of gliclazide or 270 mg/day of nateglinide and showed relatively good glycemic control (HbA_{1c} less than 7%), and we compared efficacy and safety between once daily gliclazide and t.i.d. nateglinide.

Comparison of the primary efficacy parameters, HbA_{1c} and GA, showed that 20 mg of gliclazide was modestly more effective than 270 mg of nateglinide. On the other hand, there was no difference of the 1,5-AG level between the two groups, possibly because of the wide variation of 1,5-AG values, or because nateglinide was more effective at reducing postprandial hyperglycemia than low dose gliclazide. It might be worth testing a dose of gliclazide with a similar potency to 270 mg of nateglinide (*i.e.*, achieving a similar HbA_{1c}) to verify which of these possibilities is

correct.

Our results showed that one problem with using gliclazide to treat early type 2 diabetes is an increase of events related to hypoglycemia. Although none of the hypoglycemic events observed during this study were severe, we have to take the possibility of an increase of hypoglycemic symptoms into account when using gliclazide instead of nateglinide in patients with early type 2 diabetes.

Gliclazide has been shown to possess antioxidant properties, such as inhibition of LDL oxidation and platelet activation [11, 12]. However, we used a low dose of gliclazide in this study and could not find any antioxidant effect as judged by measurement of oxidative stress markers. This suggests that the dosage we employed was too low to show any antioxidant activity in the clinical setting.

In this study, we did not randomize the groups in this study. However, it would have been preferable to enroll patients treated with either gliclazide or nateglinide who were randomly assigned to one of the two groups. Such a large scale study would be useful to evaluate the effect of gliclazide more accurately.

In conclusion, an oral dose of 20 mg of gliclazide once daily shows modestly superior efficacy relative to nateglinide for the treatment of early type 2 diabetes. On the other hand, once daily gliclazide increased the

occurrence of hypoglycemic symptoms, although it did not cause severe hypoglycemic events. Due to the increasing number of the patients with type 2 diabetes, we have to consider not only pharmacologic effects but also background factors such as economic status

and lifestyle when choosing the most suitable drug for each patient. The information obtained by our study should assist physicians to find more suitable drugs for their patients.

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