Initial Phase II Clinical Studies on Midaglizole (DG-5128)

A New Hypoglycemic Agent

S. KAWAZU, M. SUZUKI, K. NEGISHI, J. ISHII, H. SANDO, H. KATAGIRI, Y. KANAZAWA, S. YAMANOUCHI, Y. AKANUMA, H. KAJINUMA, K. SUZUKI, K. WATANABE, T. ITOH, T. KOBAYASHI, AND K. KOSAKA

SUMMARY

Midaglizole (DG-5128), 2-[2-(4,5-dihydro-1*H*-imidazol-2-yl)-1-phenylethyl]pyridine dihydrochloride sesquihydrate, is a new type of oral antidiabetic agent that has an α_2-adrenoceptor–antagonizing effect. As previously reported, midaglizole reduces plasma glucose, mainly by stimulation of insulin secretion, and inhibits epinephrine-induced platelet aggregation in normal human subjects.

In this study, the clinical safety and efficacy of short-term administration of midaglizole were evaluated in 47 patients with non-insulin-dependent diabetes mellitus (NIDDM). After an observation period on diet or sulfonylurea treatment (1 patient was on insulin), patients received 150–250 mg 3 times a day of midaglizole for 2–4 wk, (some patients continued treatment for >4 wk).

In 20 of the patients first treated with diet and then switched to midaglizole treatment, fasting plasma glucose (FPG) decreased significantly from 187 ± 10 mg/dl (mean ± SE) to 147 ± 13 mg/dl ($P < .05$) and 120 ± 6 mg/dl ($P < .01$) 2 and 4 wk, respectively, after administration of midaglizole. Glycosylated hemoglobin (HbA_1) also decreased from 12.0 ± 0.7 to 11.3 ± 1.1 and 10.7 ± 0.6% after 2 and 4 wk, respectively. In 23 of the patients whose treatment was changed from sulfonylureas to midaglizole, FPG, and HbA_1 levels were maintained at the same values obtained before administration of midaglizole. In patients treated with midaglizole for >12 wk, FPG and HbA_1 were kept at the lowered levels.

Moreover, midaglizole treatment showed a clear inhibitory effect on postprandial hyperglycemia and on FPG, reflecting the general improvement in the daily plasma glucose curve with significantly reduced fluctuation. In the oral glucose tolerance test, midaglizole significantly improved glucose tolerance, potentiated insulin secretion, and tended to depress glucagon secretion.

No abnormal findings attributable to midaglizole were noted in clinical and laboratory examinations, except for diarrhea and soft stools in 4 cases (8.5%) out of 47. No hypoglycemic symptoms were observed in this trial.

Thus, midaglizole is clinically effective for NIDDM because it improves the daily plasma gluocse curve, with decreased fasting and postprandial hyperglycemia, in addition to amelioration of oral glucose tolerance accompanied by accelerated insulin secretion.
***Diabetes* 36:221–26, 1987**

Midaglizole (DG-5128), 2-[2-(4,5-dihydro-1*H*-imidazol-2-yl)-1-phenylethyl]pyridine dihydrochloride sesquihydrate (Daiichi Seiyaku, Tokyo, Japan), is a new type of oral antidiabetic agent. Its chemical structure and modes of action are different from those of conventional sulfonylurea agents or biguanide derivatives.

It has been reported that midaglizole has a selective α_2-adrenoceptor–antagonizing effect (1–3). Midaglizole decreases blood glucose in normal rats, mice, dogs, monkeys, and mice with hereditary diabetes mellitus (A^yKK mice) (4). It accelerates insulin secretion from isolated Langerhans islets of rats (5–8) and simultaneously inhibits glucagon secretion.

As described in the previous report on the phase I clinical study in healthy subjects (9), midaglizole caused a dose-responsive hypoglycemic effect, and acceleration of insulin secretion, and a slight inhibition of glucagon secretion. Moreover, midaglizole inhibited the aggregation of platelets induced by epinephrine. Midaglizole is so rapidly absorbed that its effects developed 30–60 min after oral administration. Its half-life in blood is ~3 h, and the plasma glucose

From the Fourth Department of Internal Medicine, Saitama Medical School, Saitama (S.K., M.S., K.N., J.I.); the National Medical Center Hospital (H.S., H.Kat.) the Third Department of Internal Medicine, Faculty of Medicine, Tokyo University (S.Y., Y.A.), the Institute for Adult Diseases, Asahi Life Foundation (H.Kaj., K.S., K.W.), and the Toranomon Hospital (T.I., T.K., K.K.), Tokyo, Japan.

Address reprint requests to Dr. Shoji Kawazu, Fourth Department of Internal Medicine, Saitama Medical School, 38 Morohongo, Moroyama, Iruma-gun, Saitama, Japan 350-04.

Received for publication 18 November 1985 and accepted in revised form 16 July 1986.

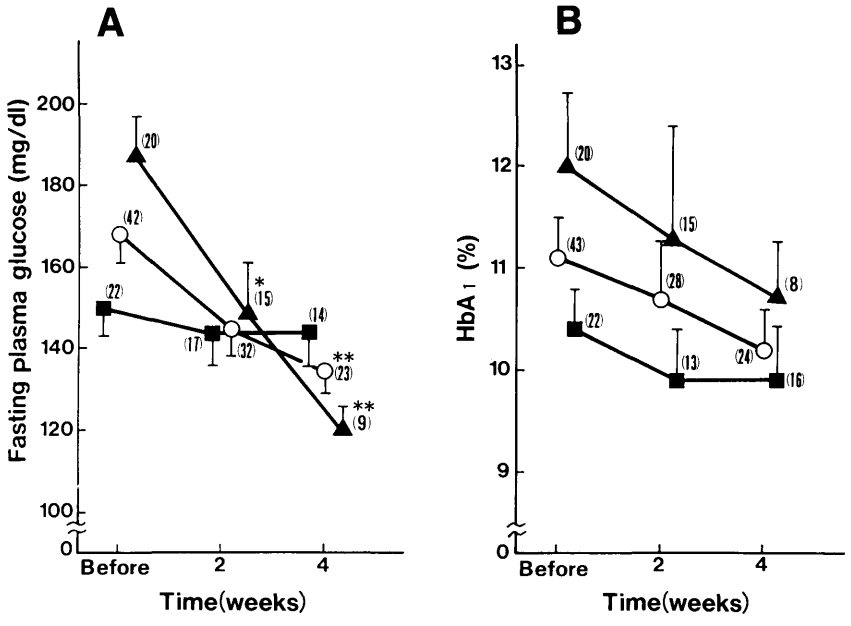

FIG. 1. Effects of midaglizole on fasting plasma glucose (*A*) and HbA_1 (*B*). Numbers in parentheses indicate number of patients at each determination point. ○, All patients; ▲, diet-DG group; ■, SU-DG group. Data represent means ± SE. Statistical analysis was performed between values before and after administration by multiple-comparison test. *$P < .05$ and **$P < .01$ vs. values before administration.

level returns to the starting level 5 h after its administration. Because its effects are shorter than those of sulfonylureas or biguanide derivatives, midaglizole is a rapid- and short-acting type of hypoglycemic agent.

In this study on midaglizole, we administered the drug for the first time to patients with non-insulin-dependent diabetes mellitus (NIDDM) to evaluate its safety, efficacy, and other characteristics.

PATIENTS AND METHODS

Forty-seven patients with NIDDM (25 men and 22 postmenopausal women; 58.7 ± 1.4 yr old; body mass index 22.3 ± 0.5; means ± SE) without serious complications participated in this study. The diagnosis of diabetes followed the criteria recommended by the Japan Diabetic Society (10,11).

Twenty patients were previously on diet therapy alone (diet-DG group), whereas 26 were treated with a sulfonylurea agent and 1 was on insulin before treatment with midaglizole. Administration of midaglizole was initiated when blood glucose levels became steady on previous therapy. In 23 of the 27 patients on drug (or insulin) therapy, the agent was changed to midaglizole (SU-DG group), 3 of the patients received both the sulfonylurea and midaglizole, and the 1 patient on insulin treatment received both insulin and midaglizole.

Midaglizole was administered in the form of tablets containing 50 or 100 mg of midaglizole. The unit dose of 150, 200, or 250 mg was administered 30 min before each meal for 2–4 wk. Changes in the dose were permitted depending on plasma glucose levels. Some patients continued midaglizole treatment for >4 wk. Before and during the study, the determinations of fasting plasma glucose (FPG), postprandial plasma glucose, HbA_1, the daily plasma glucose curve, and oral glucose tolerance tests (75 g) were performed. Any subjective and objective symptoms were recorded, and clinical and laboratory examinations, including blood pressure, heart rate, and ECG, were also carried out.

Plasma glucose, HbA_1, and circulating insulin (IRI) and glucagon (IRG) levels were determined by the glucose oxidase method, the minicolumn method (Quick-sep, Seika-

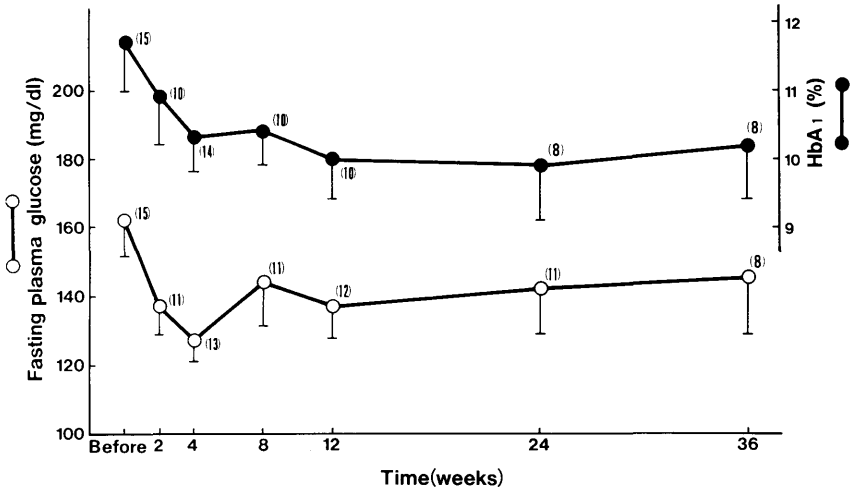

FIG. 2. Effects of midaglizole on fasting plasma glucose (○) and HbA_1 (●) in long-term administration (between 12 and 36 wk). Numbers in parentheses indicate number of patients at each determination point. Data represent means ± SE. Statistical analysis was performed between values before and after administration by multiple-comparison test.

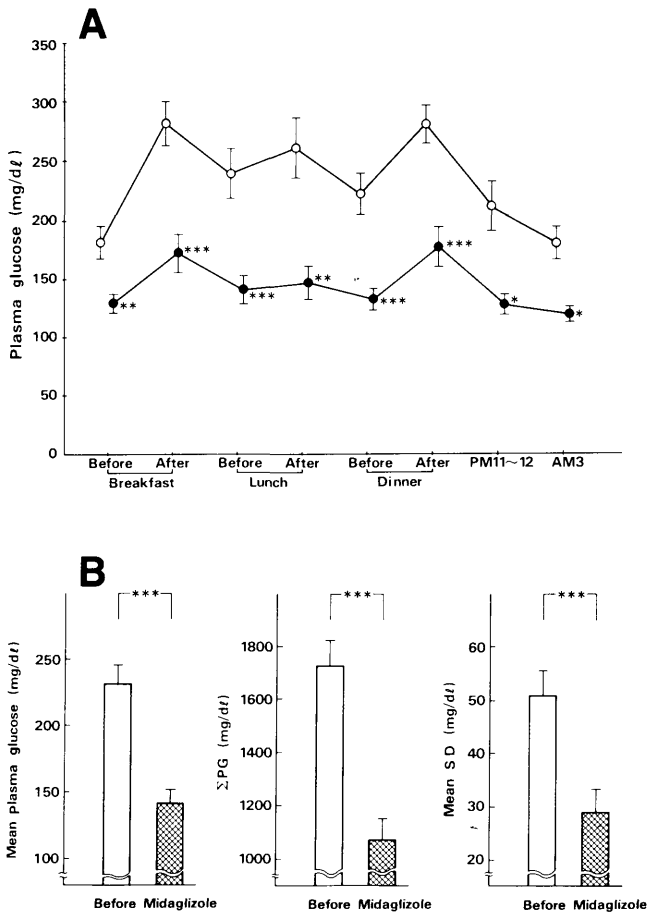

FIG. 3. Effect of midaglizole on daily plasma glucose curve (*A*). Means and sums of daily plasma glucose and mean standard deviations (SD) of daily variations (*B*). ○, Before administration; ●, after midaglizole administration (*N* = 10). Data represent means ± SE. Statistical analysis was performed between values before and after administration by multiple-comparison test. **P* < .05, ***P* = .01, and ****P* < .001 vs. values before administration.

gaku Kogyo, Tokyo), or the HPLC method (Auto A1C, Kyoto Daiichi Kagaku, Kyoto) and by radioimmunoassay with the double-antibody method (12) with human insulin and porcine glucagon as standards, respectively. All the data are expressed as means ± SE.

Statistical analysis of the data was performed with the Student's *t* test (paired) or multiple-comparison test, when appropriate, as indicated in each table and figure.

This study was conducted from November 1983 to November 1984.

RESULTS

Effects of midaglizole on FPG and HbA_1. Midaglizole was administered to 43 patients with NIDDM after they had undergone an observation period on diet therapy or sulfonylurea agents to induce a steady state. FPG decreased significantly from 168 ± 7 mg/dl before trial to 145 ± 7 and 135 ± 6 mg/dl ($P < .01$) after 2 and 4 wk, respectively. HbA_1 also tended to decrease, from 11.1 ± 0.4% before trial to 10.7 ± 0.6 after 2 wk and 10.2 ± 0.4% after 4 wk. In 20 of those in the diet-DG group, FPG and HbA_1 significantly decreased from 187 ± 10 mg/dl before trial to 147 ± 13 after 2 wk ($P < .05$) and 120 ± 6 mg/dl after 4 wk ($P < .01$) and from 12.0 ± 0.7% before to 11.3 ± 1.1 and 10.7 ± 0.6%, respectively. In the 22 patients in the SU-DG group, FPG and HbA_1 were maintained at almost the same levels obtained with the previous treatment (Fig. 1).

In 15 patients treated only with midaglizole for >12 wk, FPG decreased from 165 ± 11 mg/dl before administration of the drug to 127 ± 7, 145 ± 13, 137 ± 9, 142 ± 13, and 145 ± 17 mg/dl at 4, 8, 12, 24, and 36 wk, respectively. HbA_1 also decreased, from 11.9 ± 0.8% before administration to 10.4 ± 0.5, 10.6 ± 0.5, 10.0 ± 0.6, 9.9 ± 0.8, and 10.2 ± 0.8% after 4, 8, 12, 24, and 36 wk, respectively (Fig. 2). In 4 cases of concomitant administration with other agents (3 cases on sulfonylureas and 1 case on insulin), FPG and HbA_1 did not change (data not presented).

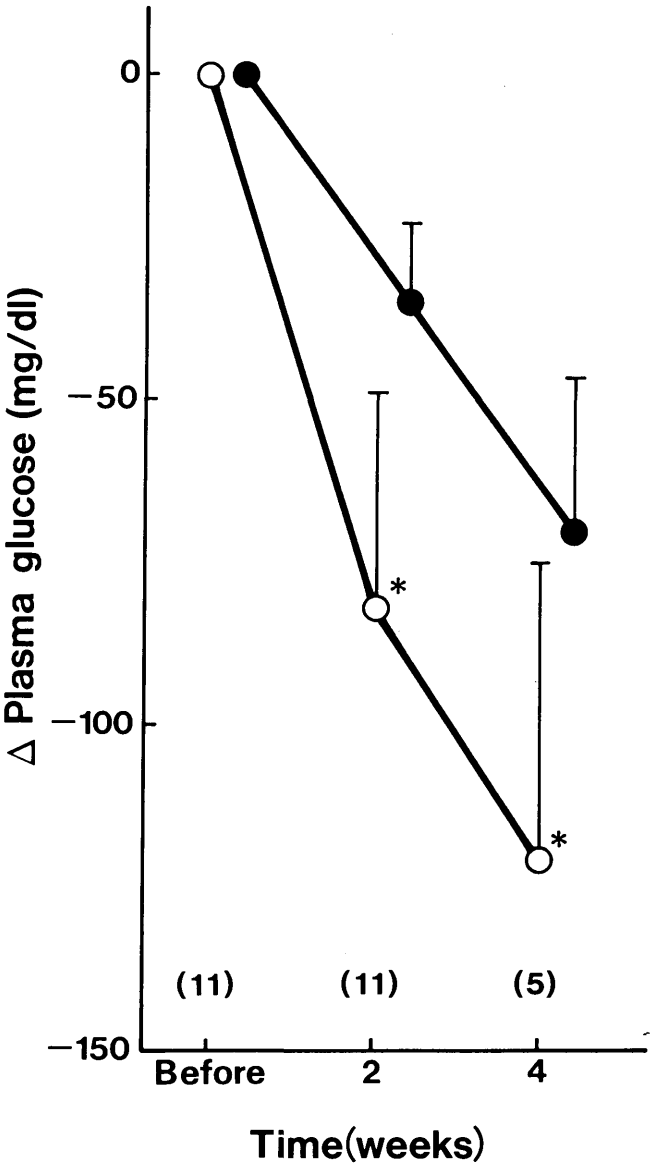

FIG. 4. Effects of midaglizole on fasting and postprandial plasma glucose in morning. Numbers in parentheses indicate number of patients at each determination point. ○, Postprandial plasma glucose; ●, fasting plasma glucose. Values are means ± SE. **P* < .05 vs. decrease of fasting plasma glucose.

Effects of midaglizole on daily plasma glucose curve. Daily plasma glucose curves before and after the administration of midaglizole were compared in 10 patients (8 cases in diet-DG group and 2 cases in SU-DG group). Significant decreases in plasma glucose levels were observed at all points (Fig. 3*A*). The means and sums of the plasma glucose levels at all determination points decreased significantly, from 231 ± 15 to 143 ± 10 mg/dl ($P < .001$) and from 1734 ± 120 to 1071 ± 87 mg/dl ($P < .001$), respectively, as a result of midaglizole administration. The standard deviation of plasma glucose also decreased significantly, from 50.8 ± 4.7 to 29.0 ± 4.1 mg/dl ($P < .001$) (Fig. 3*B*).

Effects of midaglizole on FPG and postprandial plasma glucose level after breakfast. Fasting plasma glucose decreased 34 ± 12 mg/dl (from 182 ± 13 to 147 ± 7, $P < .05$) and 70 ± 35 mg/dl (from 182 ± 13 to 115 ± 9, NS) after 2 and 4 wk of administration, respectively. On the other hand, the decreases in postprandial plasma glucose were 82 ± 22 mg/dl (from 283 ± 15 to 201 ± 12, $P < .01$) and 121 ± 46 mg/dl (from 283 ± 15 to 152 ± 26, NS) 2 and 4 wk after administration, respectively. The decreases in postprandial plasma glucose were greater than those in FPG, and the differences were statistically significant ($P < .05$) at both observation times (Fig. 4).

Effect of midaglizole on 75-g oral glucose tolerance test. In 16 patients, a 75-g oral glucose tolerance test was carried out before and after the administration of midaglizole (11 cases from diet-DG group and 5 cases from SU-DG group). IRI and IRG were also determined in these 16 patients. The glucose tolerance curve was obviously improved after midaglizole administration, showing a significant increase in IRI 30 and 180 min after glucose challenge. The circulating IRG level was lower at all points, but the difference was not statistically significant (Fig. 5). The totals of the values for glucose, IRI, and IRG in the tolerance test before and after midaglizole administration were as follows: glucose, from 1880 ± 125 to 1480 ± 101 mg/dl ($P < .01$, $N = 16$); IRI, from 103 ± 12 to 155 ± 18 μU/ml ($P < .01$, $N = 15$); and IRG, from 343 ± 87 to 301 ± 39 pg/ml (NS, $N = 5$).

Safety and side effects. The results of laboratory examinations are shown in Table 1. No abnormal values attributable to midaglizole were observed. Soft stools and diarrhea were experienced by 4 of the 47 patients (8.5%; 1 was treated with 2.5 mg of glyburide in combination, and 3 were treated with midaglizole alone). Administration of midaglizole was stopped in 3 patients; in the 4th, the diarrhea disappeared during the administration. Three patients complained of either mild heartburn, palpitations (which disappeared during administration), or breathlessness. There were no significant changes in blood pressure, heart rate, or ECG (data not presented). No patient showed a hypoglycemic reaction at any time during this study.

DISCUSSION

Preclinical experiments have revealed that midaglizole selectively antagonizes α_2-adrenoceptors (1–3). As already described in many reports on the autonomic neural regulation of Langerhans islets, stimulation of α-adrenoceptors is known to inhibit insulin secretion but accelerate glucagon secretion (13–15). Recently, the importance of α_2-adreno-

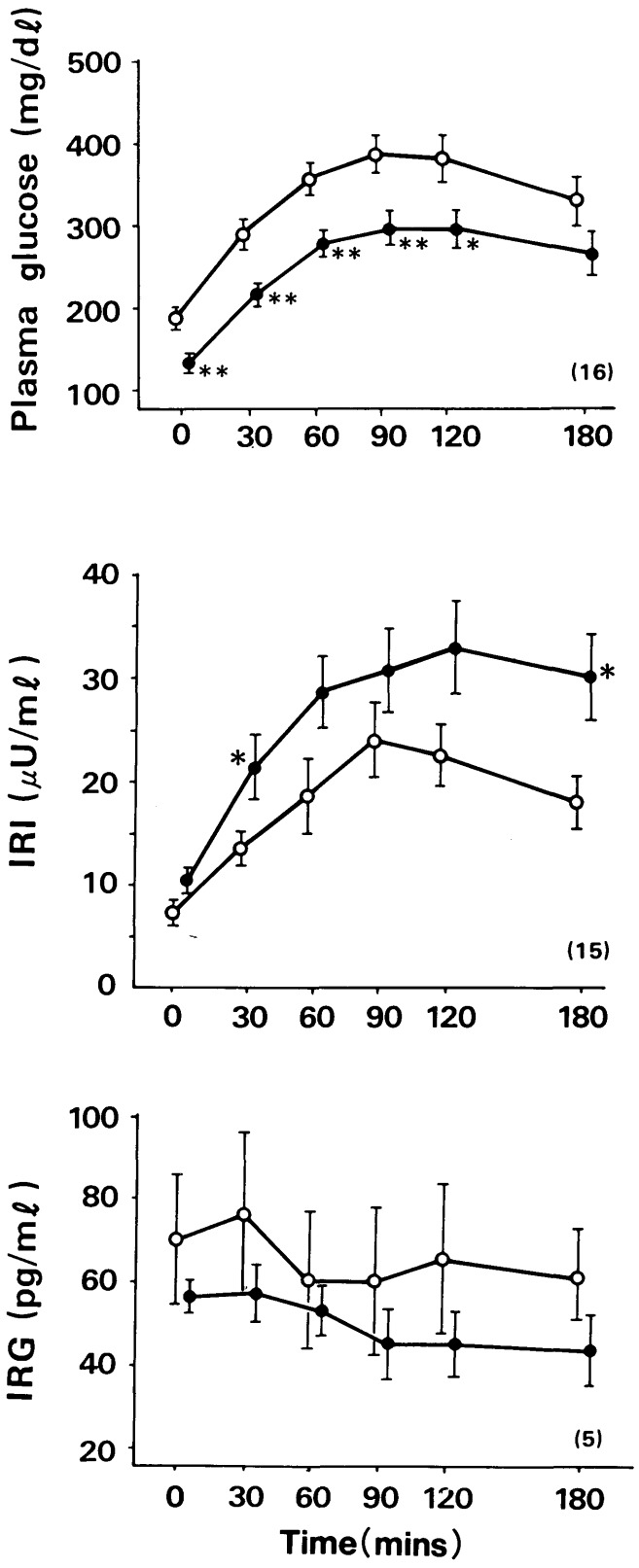

FIG. 5. Effects of midaglizole on plasma glucose, immunoreactive insulin (IRI), and immunoreactive glucagon (IRG) levels in 75-g oral glucose tolerance tests. Numbers in parentheses indicate number of patients examined. ○, Before administration; ●, after midaglizole administration. Values are means ± SE. *$P < .05$ and **$P < .01$ vs. values before administration.

TABLE 1
Laboratory examinations of patients given midaglizole alone

	Before	2 wk	4 wk	8 wk	12 wk	24 wk	36 wk
Hemoglobin (g/dl)	14.0 ± 0.2 (38)	13.8 ± 0.3 (17)	13.9 ± 0.3 (17)	13.9 ± 0.6 (4)	15.4 ± 0.8 (3)	18.0 (1)	12.0 (1)
Red blood cells (10^4/mm^3)	453.4 ± 6.8 (38)	451.6 ± 9.8 (17)	450.2 ± 7.7 (17)	447.3 ± 22.3 (4)	489.3 ± 25.1 (3)	497.0 (1)	383.0 (1)
White blood cells (10^2/mm^3)	59.5 ± 2.3 (38)	61.4 ± 3.6 (17)	61.6 ± 3.2 (17)	58.8 ± 4.0 (4)	66.0 ± 2.5 (3)	67.0 (1)	75.0 (1)
Hematocrit (%)	41.6 ± 0.8 (38)	41.5 ± 1.1 (17)	41.7 ± 0.8 (17)	41.3 ± 2.5 (4)	46.5 ± 2.5 (3)	43.8 (1)	34.9 (1)
Platelets (10^4/mm^3)	22.0 ± 0.8 (36)	20.5 ± 1.2 (13)	24.3 ± 1.9 (13)	26.3 ± 3.0 (4)	23.0 ± 3.0 (3)	25.5 (1)	33.1 (1)
Glutamic oxaloacetic transaminase (U)	18.1 ± 1.2 (41)	18.1 ± 1.5 (22)	16.9 ± 1.5 (23)	19.5 ± 2.1 (12)	45.9 ± 22.6 (7)	31.9 ± 10.8 (8)	22.9 ± 5.3 (7)
Glutamic pyruvic transaminase (U)	22.0 ± 2.7 (41)	26.5 ± 4.8 (22)	16.4 ± 2.3 (23)	25.3 ± 4.6 (12)	28.0 ± 5.9 (7)	31.4 ± 9.4 (8)	25.4 ± 8.7 (7)
Alkaline phosphatase (KAU)	6.8 ± 0.3 (41)	6.5 ± 0.4* (22)	7.1 ± 0.4 (23)	7.6 ± 0.6 (12)	8.8 ± 1.0 (8)	7.7 ± 0.8 (8)	7.6 ± 1.1 (6)
Blood urea nitrogen (mg/dl)	16.4 ± 0.7 (40)	15.0 ± 0.9* (23)	16.2 ± 1.0 (22)	13.3 ± 0.7 (12)	16.6 ± 0.9 (7)	15.6 ± 2.3 (8)	16.0 ± 1.0 (7)
Creatinine (mg/dl)	0.94 ± 0.04 (40)	0.99 ± 0.06 (23)	0.93 ± 0.06 (22)	0.90 ± 0.03 (12)	0.99 ± 0.10 (7)	0.89 ± 0.08 (7)	0.88 ± 0.07 (8)
Uric acid (mg/dl)	4.5 ± 0.3 (40)	5.1 ± 0.3 (22)	4.8 ± 0.3 (22)	4.8 ± 0.3 (11)	4.9 ± 0.3 (7)	5.1 ± 0.3 (8)	5.0 ± 0.3 (7)
Total cholesterol (mg/dl)	213.4 ± 8.4 (42)	213.2 ± 14.8 (23)	216.7 ± 9.2 (23)	217.7 ± 8.5* (12)	239.3 ± 14.3 (7)	248.0 ± 10.9 (8)	238.4 ± 15.4 (7)
Triglyceride (mg/dl)	139.3 ± 16.5 (42)	123.3 ± 14.8 (23)	151.9 ± 21.5 (23)	157.9 ± 20.3 (12)	168.2 ± 32.5 (6)	160.8 ± 17.5 (8)	150.1 ± 19.3 (7)

None of the values are outside normal limits. Numbers in parentheses are number of patients at each determination point. Data are means ± SE. Statistical analysis was performed between values before and after administration by multiple-comparison test.
*$P < .05$ vs. before administration.

ceptors in the regulation of the endocrine pancreas has been emphasized (7,16–18).

Midaglizole, as well as yohimbine, restored insulin secretion inhibited by epinephrine to a normal level (6,7). Midaglizole also antagonized the suppression of cAMP levels by epinephrine. More interestingly, there is an earlier work that demonstrates that α-adrenergic antagonists improve insulin secretion in NIDDM (19). These results suggest that the hypoglycemic effect of midaglizole is at least partly attributable to its stimulation of insulin secretion through an α_2-antagonizing effect.

To date, sulfonylureas and biguanides have been widely used as oral hypoglycemics, although the use of the latter is discouraged by the risk of lactic acidosis. Sulfonylureas such as tolbutamide, glyburide, and gliclazide are reported to exert their effects substantially by accelerating insulin secretion from the endocrine pancreas (20,21).

In this report, the hypoglycemic effect of midaglizole was studied clinically, and it was confirmed that plasma glucose and HbA_1 levels in patients with NIDDM previously treated with diet therapy significantly decreased 2 and 4 wk after administration of the drug. In patients whose treatments were changed from sulfonylureas to midaglizole, plasma glucose was maintained at almost the same level, indicating a certain degree of similarity in their effects. In patients treated for >12 wk, the hypoglycemic effect of midaglizole was clearly noted, i.e., FPG and HbA_1 were maintained at a lowered level.

Midaglizole significantly reduced the postprandial plasma glucose as well as FPG. In 11 patients, the decreases in postprandial plasma glucose were significantly greater than those in FPG at 2 and 4 wk after administration. These results suggest that the wide daily variations or the postprandial hyperglycemia often encountered in diabetics could be effectively minimized by midaglizole treatment. In fact, with the significant improvements in both the means and the sums of the daily plasma glucose curve, its variation (SD value) clearly decreased after midaglizole administration. This finding indicates that this agent prevents postprandial hyperglycemia and makes the daily plasma glucose curve more even. These findings may be explained by the fact that midaglizole is rapidly absorbed after oral administration, reaching its peak blood level after ~1 h. Clearance of midaglizole from the urine is also rapid, and the excretion rate reaches ~50% (unchanged substance) ~6 h after oral administration, which is several times faster than that of glyburide (22). These characteristics would also be advantageous in relation to drug safety.

Oral glucose tolerance tests before and after the administration of midaglizole revealed that the plasma glucose levels fell significantly at all points except 180 min and that insulin secretion was evidently accelerated. Glucagon secretion tended to be inhibited, although without significance. Nevertheless, glucagon may be partly involved in improving the glucose tolerance because midaglizole inhibited glucagon secretion from the Langerhans islets in vitro (7). Its effects on endocrine glands other than the endocrine pancreas are now under investigation.

In this study, the patients were on diet therapy throughout the observation period. Although the effect of the underlying

diet therapy and the body weight loss were not always negligible (from 54.9 ± 1.3 kg before to 54.4 ± 1.7 kg after 4 wk) the decline of FPG and HbA_1 was attributable to midaglizole because it was administered after the blood glucose levels had reached steady state. Moreover, the effects of midaglizole on plasma glucose, HbA_1, and the endocrine pancreas observed in this study were comparable with those in the phase I study (9).

Because the life expectancies of diabetics have increased recently, the major concern of treatment has shifted to the prevention or inhibition of the aggravation of diabetic complications, especially microangiopathy. This is why more strict control of plasma glucose is required. For this purpose, midaglizole would be a fertile agent, considering its inhibitory effect on the aggregation of platelets in addition to its possible regulatory effects on plasma glucose in NIDDM.

Midaglizole inhibits platelet aggregation induced by epinephrine in normal humans (9). Its effect on the aggregation of platelets in diabetics shortly after its administration also seems to be possible, although its effects during long-term administration must be investigated.

The soft stools and diarrhea observed in 4 (8.5%) of 47 patients could be related to antagonism of α_2-adrenoceptors by midaglizole (23). There were no clinically significant findings in laboratory examinations, nor was there any case of allergy or hypoglycemic reaction. Some of the sulfonylurea agents have long half-lives, and the risk of inducing hypoglycemic shock in elderly patients has been pointed out (21). Midaglizole is thought to involve a relatively low risk.

In conclusion, midaglizole is a new type of oral hypoglycemic agent that is effective in the treatment of NIDDM. When improvement of glucose metabolism and inhibition of platelet aggregation are considered, midaglizole is a candidate for better NIDDM management. Thus, midaglizole deserves further study.

REFERENCES

1. Muramatsu I, Oshita M, Yamanaka K: Selective alpha-2 blocking action of DG-5128 in the dog mesenteric artery and rat vas deferens. *J Pharmacol Exp Ther* 227:194–98, 1983
2. Yamanaka K, Kigoshi S, Muramatsu I: The selectivity of DG-5128 as an α_2-adrenoceptor antagonist. *Eur J Pharmacol* 105:625–28, 1984
3. Yamanaka K, Kigoshi S, Muramatsu I: Selective interaction of DG-5128 with a low agonist affinity state of alpha-2 adrenoceptor. *Jpn J Pharmacol* 37:293–95, 1985
4. Kameda K, Ono S, Abiko Y: Hypoglycemic action of 2-[2-(4,5-dihydro-1*H*-imidazol-2-yl)-1-phenylethyl]pyridine dihydrocloride sesquihydrate (DG-5128), a new hypoglycemic agent. *Arzneim Forsch Drug Res* 32:39–44, 1982
5. Kameda K, Koyama I, Abiko Y: Comparative study on the effects of a hypoglycemic 2-substituted-2-imidazoline derivative (DG-5128) and tolbutamide on insulin secretion from and insulin synthesis in the isolated rat pancreatic islets. *Biochim Biophys Acta* 677:263–68, 1981
6. Kameda K, Ono S, Koyama I, Abiko Y: Insulin releasing action of 2-[2-(4,5-dihydro-1*H*-imidazol-2-yl)-1-phenylethyl]pyridine dihydrochloride sesquihydrate (DG-5128), a new orally effective hypoglycemic agent. *Acta Endocrinol* 99:410–15, 1982
7. Kawazu S, Suzuki M, Watanabe T, Ishii J: α_2-Adrenergic receptor and regulation of insulin and glucagon secretion from rat isolated islets—special references to the effects of DG-5128, a new hypoglycemic drug (in Japanese). *J Jpn Diabetes Soc* 27:803–806, 1984
8. Ono S, Kameda K, Tomikawa M: Effects of new hypoglycemic drug DG-5128, α_2-adrenoceptor antagonist, on insulin release (in Japanese). *J Jpn Diabetes Soc* 28:401, 1985
9. Kawazu S, Suzuki M, Negishi K, Ishii J: Studies of midaglizole (DG-5128) in healthy subjects: a new type of oral hypoglycemic drug. *Diabetes* 36:216–20, 1987
10. Kosaka K, Akanuma Y, Goto Y, Hagura R, Hirata Y, Kawade R, Kuzuya T, Mimura G, Nakayama H, Sakamoto N, Shigeta Y: Report from the committee on diagnosis of diabetes mellitus (in Japanese). *J Jpn Diabetes Soc* 25:859–66, 1982
11. Kadowaki T, Miyake Y, Hagura R, Akanuma Y, Kajinuma H, Kuzuya N, Takaku F, Kosaka K: Risk factors for worsening to diabetes in subjects with impaired glucose tolerance. *Diabetologia* 26:44–49, 1984
12. Morgan CR, Lazarow A: Immunoassay of insulin: two antibody system. Plasma insulin levels of normal, subdiabetic and diabetic rats. *Diabetes* 12:115–26, 1963
13. Kosaka K, Ide T, Kuzuya T, Miki E, Kuzuya N, Okinaka S: Insulin-like activity in pancreatic vein blood after glucose loading and epinephrine hyperglycemia. *Endocrinology* 75:9–14, 1964
14. Porte D Jr: A receptor mechanism for the inhibition of insulin release by epinephrine in man. *J Clin Invest* 46:86–94, 1967
15. Samols E, Weir GC: Adrenergic modulation of pancreatic A, B, and D cells. *J Clin Invest* 63:230–38, 1979
16. Nakadate T, Nakaki T, Muraki T, Kato R: Adrenergic regulation of blood glucose levels: possible involvement of post synaptic alpha-2 type adrenergic receptors regulating insulin release. *J Pharmacol Exp Ther* 215:226–30, 1980
17. Nakaki T, Nakadate T, Kato R: α_2-Adrenoreceptors modulating insulin release from isolated pancreatic islets. *Naunyn-Schmiedebergs Arch Pharmacol* 313:151–53, 1980
18. Knudtzon J: Effects of selective adrenergic blocking drugs on the in vivo adrenergic effects on plasma levels of glucagon, insulin and glucose in rabbits. *Diabetologia* 25:171, 1983
19. Robertson RP, Halter JB, Porte D Jr: A role of alpha-adrenergic receptors in abnormal insulin secretion in diabetes mellitus. *J Clin Invest* 57:791–95, 1967
20. Yalow RS, Black H, Villazon M, Berson SA: Comparison of plasma insulin levels following administration of tolbutamide and glucose. *Diabetes* 9:356–62, 1960
21. Skillman TG, Feldman JM: The pharmacology of sulfonylureas. *Am J Med* 70:361–72, 1981
22. Schmidt HAE, Petrides PI: Glucose- und HB419-Konzentration im Blut sowie HB-419-Ausscheidung im Urin nach einmaliger Oraler application von HB-419-^{14}C. *Arzneim-Forsch/Drug Res* 19:1422–28, 1969
23. Field M, McColl I: Ion transport in rabbit mucosa. III. Effects of catecholamines. *Am J Physiol* 225:852–57, 1973