Studies of Midaglizole (DG-5128)

A New Type of Oral Hypoglycemic Drug in Healthy Subjects

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SUMMARY

Midaglizole (DG-5128), 2-[2-(4,5-dihydro-1*H*-imidazol-2-yl)-1-phenylethyl]pyridine dihydrochloride sesquihydrate, is a novel α_2-adrenoceptor antagonist. Its effects on plasma glucose, immunoreactive insulin (IRI), and immunoreactive glucagon (IRG) in healthy male volunteers were investigated.

Volunteers received single oral administrations of midaglizole (150–500 mg), multiple increasing oral administrations on 3 separate days (150–300 mg 3 times daily), or successive daily oral administration for 1 wk (200 mg 3 times daily).

The hypoglycemic action of midaglizole was observed within 0.5–1.0 h after its administration and thereafter for 5 h. The maximum hypoglycemic effect was found 1.0–1.5 h after administration. Midaglizole decreased postprandial hyperglycemia in a dose-dependent manner. In the fasting state, midaglizole significantly increased IRI secretion and suppressed IRG secretion. Midaglizole inhibited epinephrine-induced platelet aggregation after successive administration for 1 wk (200 mg 3 times daily).

The plasma half-life of midaglizole was only 3 h, and the drug was rapidly excreted into the urine and feces, with >80% in its unchanged form, within 24 h.

Midaglizole did not affect the results of any clinical or laboratory tests performed. Our data indicate that midaglizole is a possible hypoglycemic agent. Further clinical investigations are required to confirm its effects on diabetes mellitus. *Diabetes* 36:216–20, 1987

Midaglizole, 2-[2-(4,5-dihydro-1*H*-imidazol-2-yl)-1-phenylethyl]pyridine dihydrochloride sesquihydrate, is a selective α_2-adrenoceptor antagonist (1,2). Animal studies have shown it to be a potent hypoglycemic and an insulin secretagogue in vitro and in vivo (3–7). Its chemical structure is different from those of conventional sulfonylureas or biguanides, as is shown in Fig. 1. Moreover, midaglizole inhibited epinephrine-induced human platelet aggregation in vitro (4).

In this study, the effects of midaglizole on plasma glucose, immunoreactive insulin (IRI), and immunoreactive glucagon (IRG) were investigated in healthy male volunteers. The pharmacokinetics of midaglizole and its possible adverse effects were examined. Its effect on platelet aggregation was also studied.

SUBJECTS AND METHODS

Subjects. Twenty-nine healthy male volunteers aged 21–52 yr (body mass index 21.8 ± 0.4, mean ± SE) were involved in this study. Before the study, they were subjected to a clinical check-up. The clinical tests included an 75-g oral glucose tolerance test. Informed consent was obtained before the study.

Methods. As shown in Table 1, the subjects were divided into 5 groups, each of which received a different total dosage. Each of the six subjects in groups 1, 2, and 3 received a single oral administration of midaglizole ranging from 150 to 500 mg. Subjects in group 4 received 3 doses ranging from 150 to 300 mg/day. In group 5, 200 mg of midaglizole was administered 3 times daily for 1 wk.

The first dose was administered at 0800 h. Twenty minutes after the administration, the subjects ate a standardized meal (~500 kcal) within 10 min. However, the drug was administered 30 min after the meal on the 5th day in group 2. The subjects in group 4 took the drug at 0800 h and then fasted for 5 h. In groups 4 and 5, the 2nd and 3rd doses were administered 20 min before lunch and dinner, respectively.

On the 1st day, no drug was administered to any group. The subjects ate a standardized meal, and control data were obtained.

Blood samples were obtained from the median cubital vein at the times scheduled for determinations of plasma glucose,

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

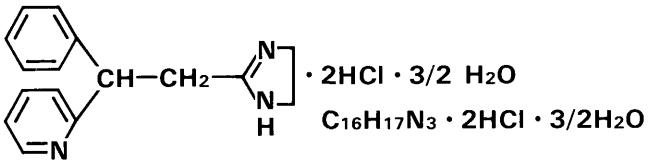

FIG. 1. Structure of midaglizole, 2-[2-(4,5-dihydro-1*H*-imidazol-2-yl)-1-phenylethyl]pyridine dihydrochloride sesquihydrate, a white, odorless, crystalline powder (351.28 M_r; melting point 131–133°C).

IRI, and IRG and for other laboratory examinations. Platelet aggregation induced by epinephrine was also measured in group 5. Clinical parameters, including blood pressure and heart rate, were also determined in each group.

Plasma glucose was determined by the glucose oxidase method. Insulin and glucagon were measured by radioimmunoassay with porcine insulin and glucagon as standards (8).

Platelet aggregation was measured by the photometric method of Born and Cross (9) on the control day and the 7th day of administration in group 5. Blood samples were obtained from the median cubital vein at 0, 2.5, and 5 h after the first administration each day. Platelet aggregation was induced by epinephrine, and the results were expressed by two parameters: *1*) the second-phase aggregation time (time required for initiation of second-phase aggregation) and *2*) the maximum rate of the second-phase aggregation.

The plasma and fecal concentrations of midaglizole were measured by gas chromatography–mass spectrometry, and the urinary concentration was measured by HPLC (10).

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

RESULTS

Effects of midaglizole on mean plasma glucose after single preprandial oral administration. Plasma glucose concentrations after breakfast were significantly suppressed by 300 and 500 mg of midaglizole in a dose-dependent manner (Fig. 2*A*). Midaglizole showed the maximum hypoglycemic effect at 1.5 h after administration. The effect of midaglizole was observed from 0.5 h until almost 5 h after administration.

Postprandial hyperglycemia observed in controls was significantly suppressed after the administration of 300 and 500 mg of midaglizole. IRI was increased slightly by midaglizole, in contrast to the obvious suppression of plasma glucose (Fig. 2*B*).

When 200 mg of midaglizole was administered 30 min after the meal (day 5 in group 2), the maximum hypoglycemic effect was less than that observed when the drug was administered before breakfast (data not shown).

Effects of midaglizole on plasma glucose, IRI, and IRG concentrations in fasting state. In group 4, the subjects fasted during the observation period (5 h beginning at 0800 h) on the control and administration days. On the control day, no significant change in plasma glucose was observed. After midaglizole administration in doses ranging from 150 to 300 mg, plasma glucose was significantly decreased in a dose-dependent manner (Fig. 3*A*).

The maximum effect was observed 1 h after midaglizole administration. IRI increased significantly 1 h after administration of 300 mg midaglizole. During the same observation period, a decrease in IRG was also observed (Fig. 3, *B* and *C*).

Effects of midaglizole on fasting plasma glucose with successive oral administration for 7 days. Midaglizole was administered at a dose of 200 mg 3 times daily for 7 days. On the 1st day of administration (day 2), significant suppression of plasma glucose was observed 1.5 h after administration; this suppression lasted >2.5 h. On the 7th day of administration (day 8), both fasting plasma glucose and postprandial hyperglycemia were significantly suppressed (Fig. 4*A*) compared with values on the control day.

Effects of midaglizole on platelet aggregation induced by epinephrine. At a dose of 200 mg 3 times daily, midaglizole significantly suppressed epinephrine-induced platelet aggregation 2.5 h after administration on day 8 (7th day of administration). In addition, the second-phase aggregation time was significantly prolonged, and the maximum rate of second-phase aggregation was suppressed 2.5 h after administration of midaglizole.

Plasma concentration of midaglizole. The diurnal variation of plasma concentration of midaglizole was obtained on days 2, 5, and 8 (1st, 4th, and 7th days of administration) of successive administration of 200 mg 3 times daily. The maximum plasma concentrations were obtained at ~1 h after each administration.

The diurnal variations on the three observation days were comparable to each other. The pattern of plasma concentration of midaglizole was unchanged throughout the study, showing 3 peaks/day (Fig. 4*B*).

Plasma half-life and urinary and fecal excretion of midaglizole. The plasma half-life of midaglizole was ~3 h, and the cumulative urinary and fecal excretion of the unchanged form of midaglizole after a single oral administration at a dose of 200 mg (group 2) were 73.0 ± 2.1 and 10.5 ± 2.7%, respectively, within 24 h.

Adverse effects of midaglizole. No substantial changes in hematology, blood biochemistry, or urinalysis were observed. No marked changes were observed in blood pressure, heart rate in an erect posture (Fig. 5), electrocar-

TABLE 1
Dose schedule

	Day							
Group	1	2	3	4	5	6	7	8
1	C	150						
2	C	200			200*			
3	C	300			500			
4	C	150†			200†			300†
5	C	200†	200†	200†	200†	200†	200†	200†

C, control day—no drug administered and subjects ate a standardized breakfast of ~500 kcal within 10 min at 0820 h. On other days, 1st dose of drug (if given) was administered at 0800 h. At 0820 h, subjects ate standardized breakfast within 10 min. On day 5 in group 2, 1st dose was administered 30 min after breakfast. In group 4, 1st dose was administered at 0800 h, and subjects fasted for 5 h on days 2, 5, and 8. Second and 3rd doses were administered 20 min before meal and dinner, respectively. In group 5, dose was administered 20 min before each meal. Six subjects per group.
*Dose was administered after breakfast.
†Dose was administered 3 times daily.

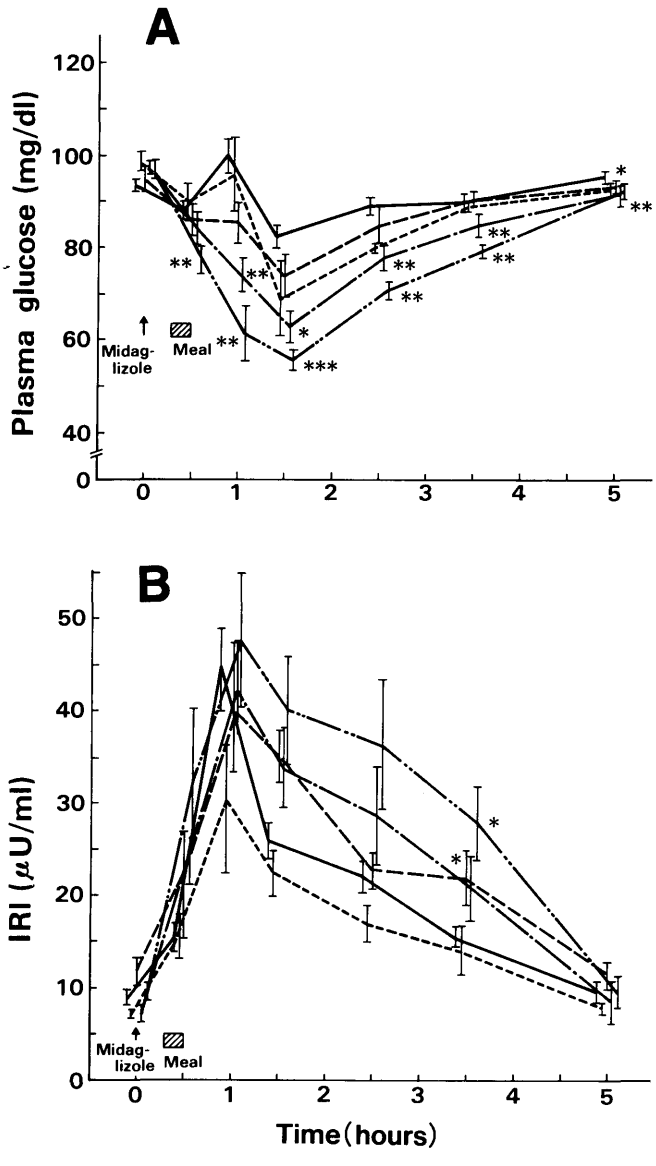

FIG. 2. Effects of single oral administration of midaglizole on plasma glucose (*A*) and insulin (IRI) (*B*) concentrations in groups 1, 2, and 3 in Table 1. Subjects ate standardized meal (500 kcal) 20 min after midaglizole administration within 10 min. Control plasma glucose and insulin concentrations are expressed as means of all estimations (*N* = 18) obtained at each sampling time on 3 control days. Statistical analysis was performed between control days and respective administration days by Student's *t* test in groups 1 and 2, and multiple-comparison test was carried out for group 3. Control (——) and 150 (-----), 200 (– –), 300 (– - –), and 500 (– - - –) mg midaglizole administrations. Data represent means ± SE (*N* = 6). **P* < .05, ***P* < .01, and ****P* < .001 vs. control values.

diogram, respiration rate, or body temperature. There were no complaints or clinical findings, except that three of six volunteers showed a slight hypoglycemic reaction between 0.5 and 1 h after a single oral dose of 500 mg.

DISCUSSION

The oral antidiabetic drugs available are all sulfonylureas or biguanides, and their clinical usefulness in non-insulin-dependent diabetics has been established. However, they are only partially effective or largely ineffective in some cases, and other types of oral hypoglycemic agents would be useful (11). Combinations of drugs can be also effective in some cases.

Midaglizole is a newly developed oral hypoglycemic agent that is completely different from sulfonylureas and biguanides in chemical structure. It antagonizes α_2-adrenoceptors (1,2) and stimulates insulin secretion in vitro and in vivo (3–7). The pioneering work on the endocrine pancreas receptor mechanisms has shown that insulin release is inhibited by stimulation of α-adrenoceptors (12–14). It has also been demonstrated that the α_2-adrenoceptor antagonist phentolamine normalizes abnormal insulin secretion in diabetes mellitus (14).

In our study with human volunteers, we found that significant decrease in plasma glucose, augmentation of circulating insulin, and suppression of circulating glucagon occur in a dose-dependent manner after the administration of midaglizole. Its effect on plasma glucose lasted for 5 h, beginning 30–60 min after administration. Midaglizole was rapidly absorbed and excreted with few metabolic changes

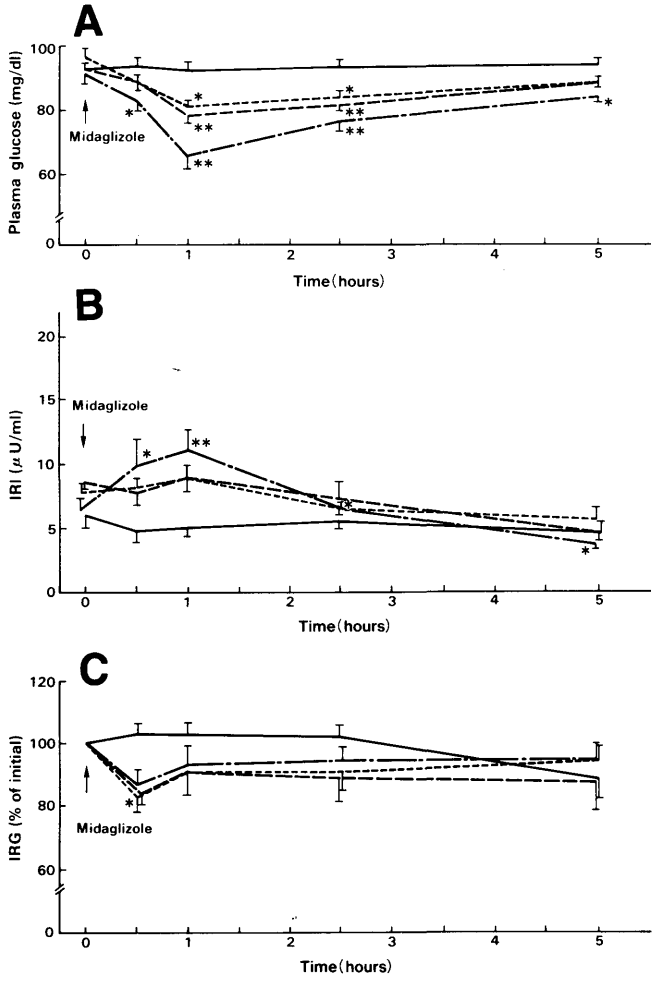

FIG. 3. Effects of midaglizole on plasma glucose (*A*), immunoreactive insulin (IRI) (*B*), and immunoreactive glucagon (IRG) (*C*) in 6 subjects (group 4 in Table 1). Subjects fasted overnight and for 5 h after drug administration. Basal IRG level in morning of control day was 234 ± 97 pg/ml. Control (——) and 150 (-----), 200 (– –), and 300 (– - –) mg midaglizole administrations. Data represent means ± SE (*N* = 6). Statistical analysis was performed between values before and after administration of drug by multiple-comparison test. **P* < .05 and ***P* < .01 vs. preadministration value.

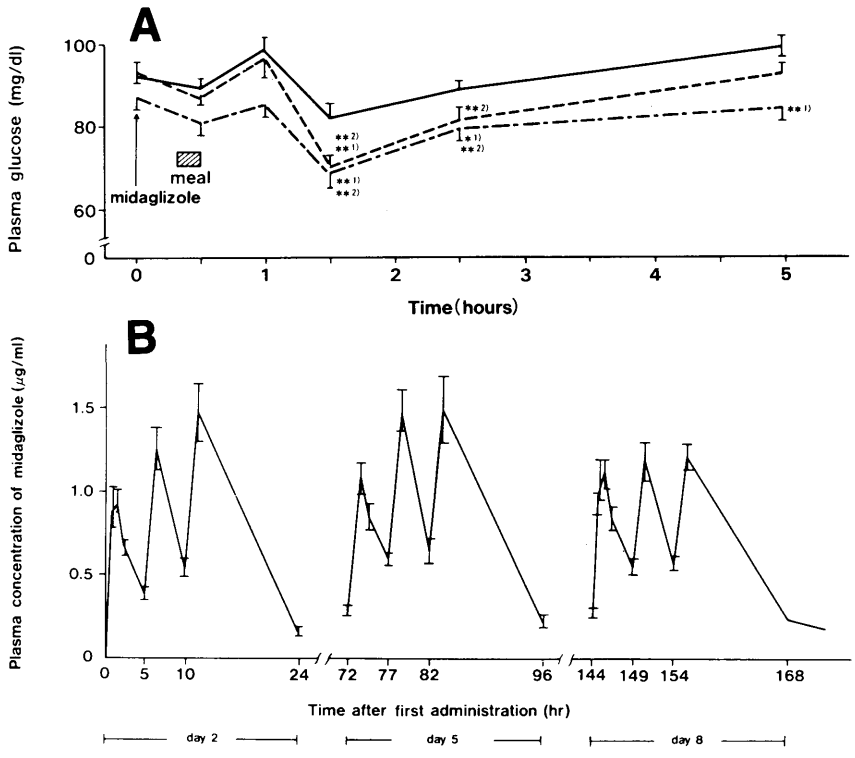

FIG. 4. *A*: effects of successive administrations of midaglizole on plasma glucose. *B*: mean plasma concentration of midaglizole. Drug was administered at dose of 200 mg 3 times daily for 7 days (but not on control day). Meals were eaten 20 min after drug administration within 10 min. Control (——), day 2 (-----), and day 8 (– - –). Days 2, 5, and 8 were 1st, 4th, and 7th days of administration, respectively. Data represent means ± SE (N = 5). Statistical analysis was performed between control day and respective administration day by multiple-comparison method. *$P < .05$ and **$P < .01$: *1*) vs. control and *2*) vs. preadministration value.

and reached the peak serum level ~1 h after oral administration. Midaglizole seems to be a rather rapid- and short-acting hypoglycemic drug compared with sulfonylureas (15).

In addition to its hypoglycemic effect, we found midaglizole to be a potent inhibitor of epinephrine-induced platelet aggregation. Because human platelets are reportedly abundant in α_2-adrenoceptors (16,17), inhibition of platelet aggregation by midaglizole may be derived from its antagonistic activity on α_2-adrenoceptors. The inhibitory effect of midaglizole on platelet aggregation could be expected to suppress the development of diabetic vascular complications.

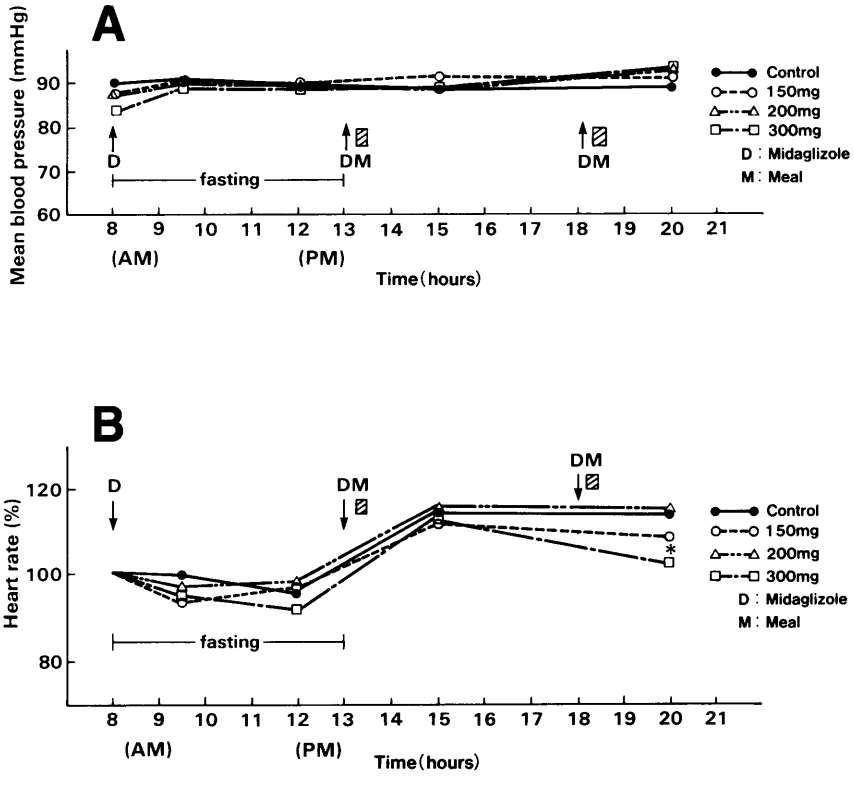

FIG. 5. Effects of midaglizole on mean blood pressure (*A*) and heart rate (*B*). Data represent means (N = 6). Statistical analysis was performed between control and respective administration day by multiple-comparison test. *$P < .05$ vs. control.

There were no significant findings in erect blood pressure, heart rate, electrocardiogram, or laboratory examinations. There were no subjective findings, except for a mild transient hypoglycemia after the maximum dose of midaglizole. No significant complaints of dizziness, nausea, headache, or other such manifestations were recorded.

The relatively short plasma half-life and the rapid excretion of midaglizole with few metabolic changes could be advantageous from the standpoint of safety (data not shown; ~50% of midaglizole was excreted in unchanged form in urine within 6 h after administration).

In conclusion, midaglizole, which is different from the sulfonylureas in chemical structure, is a potent rapid- and short-acting hypoglycemic drug in humans.

ACKNOWLEDGMENT

This report was presented in abstract form at a poster session of the American Diabetes Association Annual Meeting in 1984 at Las Vegas.

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