Effect of an Oral α₂-Adrenergic Blocker (MK-912) on Pancreatic Islet Function in Non–Insulin-Dependent Diabetes Mellitus

F. Javier Ortiz-Alonso, William H. Herman, Barry J. Gertz, Vanessa C. Williams, Marla J. Smith, and Jeffrey B. Halter

We used MK-912, a potent new selective α₂-adrenergic receptor antagonist that is active orally, to study the effect of short-term, selective α₂-blockade on fasting plasma glucose (FPG) and pancreatic islet function in non–insulin-dependent diabetes (NIDDM). Ten asymptomatic patients with NIDDM received either a single oral dose of MK-912 (2 mg) or placebo in a double-blind, cross-over study. B-cell function was measured by the acute insulin response (AIR) to glucose (1.66 mmol/kg intravenously [IV]) and by the AIR to arginine (5 g IV) during a hyperglycemic glucose clamp at a mean glucose level of 32.1 mmol/L to provide an estimation of maximal B-cell secretory capacity. A-cell function was estimated by the acute glucagon response (AGR) to arginine during the glucose clamp. Effective α₂-adrenergic blockade was apparently achieved, as there were substantial increases of plasma norepinephrine (NE) ($P < .01$) and both systolic blood pressure (SBP) ($P < .01$) and diastolic blood pressure (DBP) ($P < .05$) after treatment with MK-912, but not after placebo. MK-912 caused a significant ($P < .05$) although modest decrease of FPG that was associated with a small increase of fasting plasma insulin ($P < 0.01$), C-peptide ($P < .05$), and glucagon ($P < .01$). FPG and hormone levels remained unchanged after placebo. MK-912 tended to increase the AIR ($P = .06$) and the C-peptide response ($P = .07$) to glucose compared with placebo. There was a small, but significant, overall treatment effect for both the AIR and AGR to arginine with MK-912 (both $P < .05$, ANOVA). These studies indicate that MK-912 causes (1) sympathetic activation consistent with effective α₂-adrenergic blockade; (2) a small decrease of FPG and a small increase of fasting plasma insulin; (3) a small improvement of B-cell function due to an increase in maximal B-cell secretory capacity; and (4) a small increase in basal and stimulated glucagon. These findings suggest that endogenous α₂-adrenergic tone may contribute, although to a small extent, to the impaired B-cell function in NIDDM. If an α₂-blocker becomes available that does not increase BP, studies would be warranted to evaluate its potential impact on glucose regulation in patients with NIDDM.
Copyright © 1991 by W.B. Saunders Company

SEVERAL ANIMAL and human studies have suggested a possible role for endogenous α-adrenergic tone in the impaired B-cell function in non–insulin-dependent diabetes (NIDDM).[1-4] Adrenergic tone could negatively influence B-cell function by a postsynaptic α₂-adrenergic receptor mechanism that inhibits insulin secretion.[5-7] Although the improvement in B-cell function in NIDDM afforded by α-adrenergic blockade was small in previous studies,[3,4] such an effect could be potentially useful in the clinical management of NIDDM. However, this would require the availability of a specific α₂-adrenergic receptor antagonist that can be administered orally.

MK-912 is a recently discovered potent and selective α₂-adrenergic receptor antagonist in both animals and humans.[8-10] Clinical studies in healthy volunteers have demonstrated a general pharmacodynamic profile for MK-912 consistent with α₂-adrenergic antagonist properties over a dose range of 0.1 to 2.0 mg orally, including a mild pressor response, an increase in circulating MHPG (3-methoxy-4-hydroxyphenylglycol) concentrations, and a mild axiogenic effect.[9] More specific characterization of its α₂-antagonist properties was achieved by blocking responses to an α₂-agonist challenge with clonidine.[10] MK-912 inhibited clonidine-induced sedation, xerostomia, growth hormone release, hypotension, bradycardia, and hyperglycemia.[10] These findings support the use of MK-912 as a probe of the pathophysiologic involvement of α₂-mediated adrenergic tone in the impaired islet cell function of NIDDM.

We used MK-912 to study the effect of short-term, selective α₂-blockade on plasma glucose levels and on pancreatic islet function in 10 patients with NIDDM in a double-blind, placebo-controlled, cross-over study. We also measured blood pressure and plasma catecholamine responses to characterize the pharmacologic activity of MK-912 in this study population.

METHODS

Subjects

Table 1 shows the clinical characteristics of the patients. Ten subjects (eight males, two females) with NIDDM were studied. Subjects were chosen with the following characteristics: (1) asymptomatic from hyperglycemia after medication was discontinued; (2) fasting plasma glucose (FPG) concentrations of 7 to 14 mmol/L (~125 to 250 mg/dL); (3) body weight not greater than 90 kg; and (4) less than 10-year history of diabetes. The presence of NIDDM was defined by National Diabetes Data Group (NDDG) criteria.[11] All patients were without evidence of retinopathy, nephropathy, neuropathy, or cardiovascular disease on physical examination, screening biochemical tests, and electrocardiogram (EKG). Patients were treated with diet alone or a sulfonylurea that was

Table 1. Clinical Characteristics of the Patients

Patient No.	Age (yr)	Duration of Diabetes (yr)	Weight (kg)	Ideal Body Weight (%)	Fasting Plasma Levels*					
					Glucose† (mmol/L)	Insulin‡ (pmol/L)	C-peptide§ (nmol/L)	Glucagon¶ (ng/L)	NE‖ (nmol/L)	EPI** (nmol/L)
1	36	2	84	118	11.2	93	0.5	146	1.3	0.5
2	44	4	78	114	13.7	44		76	0.8	0.5
3	46	3	80	113	13.6	75	0.7	159	0.9	0.5
4	48	1	67	104	7.1	57	0.6	157	1.1	0.6
5	48	1	74	109	9.4	78	0.8	159	1.5	0.4
6	49	4	77	140	14.6	81	0.5	290	1.1	0.7
7	50	3	89	123	11.1	66	0.3	74	0.6	0.3
8	52	2	75	109	12.7	71	0.7	38	0.9	0.3
9	58	3	85	138	11.7	116		85	0.6	0.5
10	60	2	74	109	8.7	91	0.8	147	1.1	0.4

*Determined as the mean of the 10-, 5-, and 0-minute, or 5- and 0-minute, values pretreatment, from both study days.
†To convert glucose values to mg/dL, multiply by 18.
‡To convert insulin values to μU/mL, multiply by 0.171.
§To convert C-peptide values to ng/mL, multiply by 3.02.
¶To convert glucagon values to pg/mL, multiply by 1.0.
‖To convert norepinephrine (NE) values to pg/mL, multiply by 169.
**To convert epinephrine (EPI) values to pg/mL, multiply by 183.

discontinued 3 weeks before the study, and on no medications that might interfere with catecholamine action. The study was approved by the Human Subjects Committee of The University of Michigan Medical Center. Informed consent was obtained from all subjects.

Study Conditions

Each patient received either a single oral dose (2.0 mg) of MK-912 or placebo in a double-blind, cross-over study. Study days were separated by 1 week. Patients were admitted to the Clinical Research Center of the University of Michigan Medical Center the night before each treatment day. They were fasting for 12 hours before treatment and refrained from taking any form of medication for a period of 2 weeks before and throughout the study period (3 weeks in the case of sulfonylurea agents). Blood samples were obtained via a catheter inserted into a superficial wrist vein. To achieve arterialization of venous blood, the hand and wrist were warmed in a wooden box thermostatically heated to 60°C. A second intravenous (IV) line for infusions and injections was inserted in the contralateral antecubital vein.

Protocol

Figure 1 shows the mean plasma insulin and glucose levels for the 10 patients during the active drug day to illustrate the protocol. The IV lines were inserted 45 to 60 minutes before treatment. At 10, 5, and 0 minutes before treatment, blood samples were obtained for baseline plasma glucose, insulin, C-peptide, and glucagon determinations. Plasma norepinephrine (NE) and epinephrine (EPI) were measured at 5 and 0 minutes before treatment. Patients then received orally a 2.0 mg dose of MK-912, or a placebo, with 150 mL of water. Thirty minutes after treatment, blood was obtained for glucose and hormone determinations. At 50, 55, and 60 minutes posttreatment, blood samples were obtained for plasma glucose and hormone measurement; plasma NE and EPI were measured at 55 and 60 minutes. At 60 minutes postdose, a bolus injection of glucose (1.66 mmol/kg) was administered over 30 seconds as a 50% glucose solution. This was immediately followed by a variable infusion rate of a 20% glucose solution plus 10 mmol/L KCl via peristaltic pump in order to reach a steady-state plasma glucose level of approximately 30.0 mmol/L. Every 5 minutes a blood sample was assayed for glucose determination by use of a Beckman portable glucose analyzer (Beckman Instru-

ments, Fullerton, CA) and the glucose infusion adjusted accordingly. Blood samples were obtained at 3, 4, 5, 7, 10, 15, 20, 25, 30, 40, 50, 55, and 60 minutes after glucose bolus for determination of glucose, insulin, and C-peptide. Glucagon was measured at 50, 55, and 60 minutes, and NE and EPI at 15, 30, 45, and 60 minutes following the glucose bolus.

Sixty minutes later (120 minutes postdose and 60 minutes into the hyperglycemic clamp), a maximally stimulating dose of 10% arginine hydrochloride (5 g IV) was administered over 30 seconds. Blood samples were obtained at 2, 3, 4, 5, and 10 minutes after arginine administration for plasma glucose and hormone determinations. The glucose clamp was maintained for 10 minutes after the arginine challenge. One week after the first study, each patient returned for the second treatment period and followed the same protocol with the appropriate agent.

Heart rate (HR) and blood pressure (BP) were monitored before and every 10 minutes after treatment for the first 3 hours, then at less frequent intervals until discharge from the study unit. A continuous single-channel EKG monitor was used to monitor the HR and rhythm. Screening biochemistry, hematology, urinalysis, and 12-lead electroencephalogram (ECG) were repeated after the final treatment for safety purposes.

Calculations

Several parameters were calculated. The mean change from baseline in plasma glucose, insulin, C-peptide, and glucagon 50 to 60 minutes after treatment was calculated. The first-phase B-cell response to glucose was calculated as the mean of the insulin levels obtained 3 to 5 minutes after the IV glucose bolus minus the mean of the three prestimulus levels. The second-phase B-cell response to glucose was calculated as the area under the insulin curve (AUC) from 10 to 60 minutes during the hyperglycemic clamp. To estimate the maximal B-cell secretory capacity, the acute insulin response (AIR) to the B-cell stimulus arginine was calculated during the steady-state glucose level of 30 mmol/L (AIR-max).[12] The AIR and the acute glucagon response (AGR) to arginine were calculated as the mean of the hormone levels obtained 2 to 5 minutes after the arginine injection minus the mean of the three prestimulus hormone levels. The effect of MK-912 on plasma NE and EPI, BP, and HR were also calculated. HR and BP responses
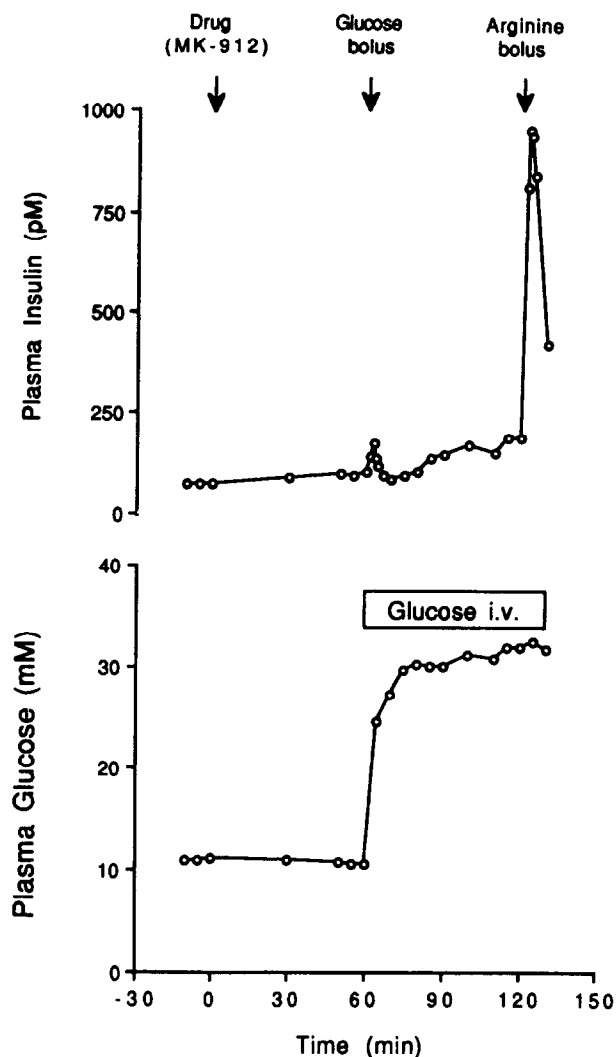
Fig 1. Mean plasma insulin and glucose levels of 10 patients with NIDDM during the MK-912 protocol day. The drug (2 mg) was administered orally at 0 minutes. At 60 minutes, a bolus injection of glucose (1.66 mmol/kg) was administered, followed by a variable glucose infusion to reach and maintain a mean steady-state plasma glucose concentration of approximately 30 mmol/L. A bolus injection of arginine (5 g IV) was administered after 60 minutes of glucose infusion, which was continued for 10 minutes following the arginine bolus. On a separate day, the subjects underwent an identical protocol in which a placebo was administered instead of MK-912. Note that plasma insulin doubles, from 95 to 181 pmol/L (between 60 and 120 minutes), when plasma glucose was increased from approximately 10 to 30 mmol/L.

are reported as the average of the three 10-minute determinations over each 30-minute interval for the first 3 hours postdose.

Analytical Methods

Plasma glucose was measured by the Michigan Diabetes Research and Training Center (MDRTC) core laboratory with the hexokinase-glucose-6-phosphate dehydrogenase reaction (Gilford Impact 400E Automated System, Oberland, OH). Plasma immunoreactive insulin (IRI) was assayed by the MDRTC laboratory using a double-antibody radioimmunoassay (RIA). Plasma immunoreactive glucagon (IRG) was assayed by the MDRTC with a double-

antibody RIA using ^{125}I trace (New England Nuclear, Boston, MA).[13] Plasma catecholamines (NE and EPI) were measured by single-isotope enzymatic assay.[14]

Statistical Analysis

Each of the parameters was compared between treatments with the ANOVA model of Grizzle that contains factors for sequence, patient within sequence, treatment, and period.[15] There was no evidence of carryover. Data are expressed as mean ± SEM. Normality assumptions were tested with the Shapiro-Wilks statistic, and Hartley's maximum F test was used to test the homogeneity of variance assumption. Results were considered significant at $P <$ .05 (two-tailed test).

RESULTS

Treatment Periods

As shown in Table 2, there were no differences in baseline plasma levels of glucose, insulin, C-peptide, glucagon, NE, and EPI between the two treatment periods. Similarly, the steady-state plasma glucose levels achieved during the hyperglycemic clamps were comparable during both drug and placebo days (31.4 ± 0.6 v 32.8 ± 0.9 mmol/L, $P =$ NS).

Effects of MK-912 on Plasma Catecholamines, BP, and HR

Figure 2 shows plasma NE and EPI levels before and for 2 hours after both treatments. MK-912 caused a significant increase over baseline in mean plasma NE (average change from baseline over 2 hours: $\Delta = +1.1 \pm 0.3$ nmol/L; $P < .01$) and EPI ($\Delta = +0.10 \pm 0.03$ nmol/L; $P < .01$). There were no significant changes in mean plasma NE ($\Delta = +0.02 \pm 0.07$ nmol/L; $P =$ NS), or EPI ($\Delta = +0.02 \pm 0.03$ nmol/L; $P =$ NS), after the administration of placebo. When these parameters were compared between treatments (MK-912 v placebo), a significant overall treatment effect was found for NE ($P < .01$) and EPI ($P < .01$).

Figure 3 illustrates systolic (SBP) and diastolic (DBP) blood pressures, measured before and for 8 hours after both treatments. Both increased significantly over baseline after MK-912, but not after the administration of placebo (average change from baseline over 8-hour observation period: ΔSBP $= +10 \pm 2$ v $+3 \pm 2$ mm Hg, $P < .01$; and ΔDBP $= +3 \pm 1 v -2 \pm 2$ mm Hg, $P < .05$). No significant changes in HR over baseline were observed after the administration of MK-912 or placebo (data not shown).

Table 2. Baseline* Fasting Levels of Plasma Glucose, and Hormones Before the Administration of Either MK-912 or Placebo

	Drug Day	Placebo Day
Plasma glucose (mmol/L)	11.0 ± 0.9	12.0 ± 0.7
Plasma insulin (pmol/L)	75 ± 6	79 ± 8
Plasma glucagon (ng/L)	122 ± 17	144 ± 33
Plasma C-peptide (nmol/L)	0.6 ± 0.1	0.6 ± 0.1
Plasma norepinephrine (nmol/L)	1.0 ± 0.1	1.0 ± 0.1
Plasma epinephrine (nmol/L)	0.5 ± 0.1	0.5 ± 0.1

NOTE. All values are mean ± SEM, N = 10.

*Baseline determined as the mean of the 10-, 5-, and 0-, or 5- and 0-minute, predose values, as appropriate.
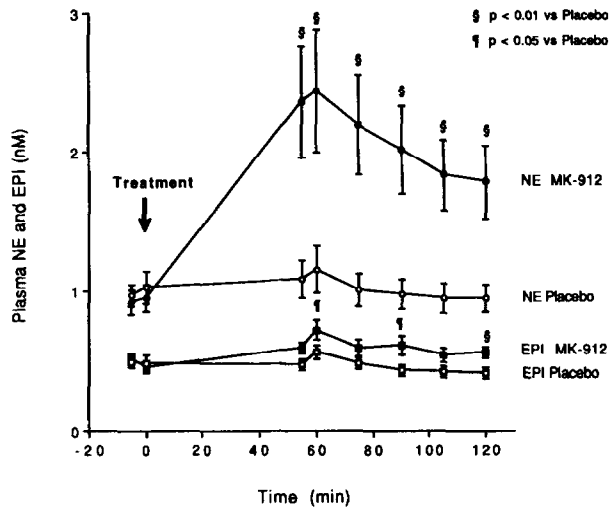
Fig 2. Plasma norepinephrine (NE) and epinephrine (EPI) levels before and over a period of 2 hours after treatment. Both mean plasma NE and EPI increased over baseline during the 2 hours after the administration of MK-912 (both $P < .01$), but not after placebo. All values are mean ± SEM, n = 10.

Effect of MK-912 on FPG and Hormone Levels

The changes from baseline for glucose, insulin, C-peptide, and glucagon were compared by ANOVA for the two treatment periods (MK-912 v placebo). A significant overall treatment effect was found for C-peptide and for glucagon (both $P < .05$), but the effects on glucose ($P = .13$) and insulin ($P = .10$) did not reach statistical significance.

Figure 4 illustrates the absolute changes from baseline for FPG and hormone levels 50 to 60 minutes after treatment and the within-treatment statistical evaluations.
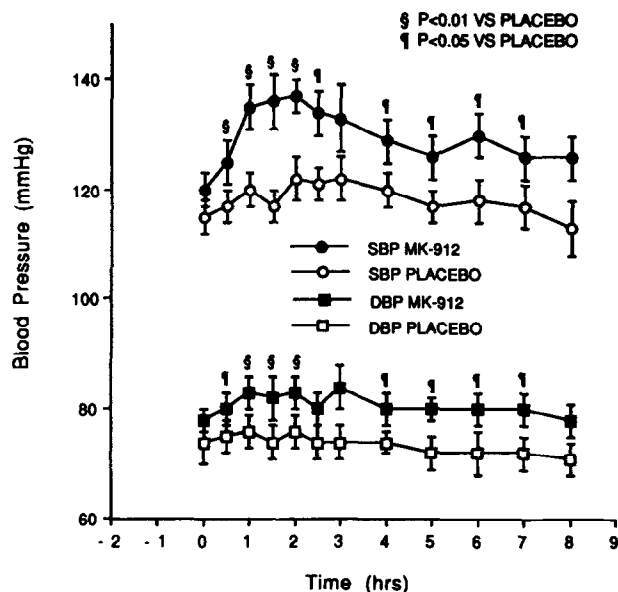

Fig 3. Systolic (SBP) and diastolic (DBP) blood pressure before and over a period of 8 hours after treatment. Patients received either MK-912 or placebo at time 0. Both SBP ($P < .01$) and DBP ($P < .05$) increased over baseline during the 8 hours after the administration of MK-912, but not after placebo. All values are mean ± SEM, n = 10.

FPG decreased slightly from baseline in nine of the 10 subjects after the administration of MK-912 ($\Delta = -0.43 \pm 0.13$ mmol/L; $P < .05$), but remained unchanged after the administration of placebo ($\Delta = -0.13 \pm 0.16$ mmol/L; $P = $ NS). Plasma insulin increased from baseline in nine of the 10 subjects after MK-912 ($\Delta = +23 \pm 6$ pmol/L; $P < .01$), but remained unchanged after placebo ($\Delta = +4 \pm 6$ pmol/L; $P = $ NS). Plasma samples for C-peptide assay were lost from two patients. Plasma C-peptide increased from baseline in seven of eight patients after MK-912 ($\Delta = +0.12 \pm 0.03$ nmol/L; $P < .05$) and remained unchanged after placebo ($\Delta = -0.02 \pm 0.03$ nmol/L; $P = $ NS). Fasting plasma glucagon increased in eight of the 10 patients after treatment with MK-912 ($\Delta = +12 \pm 4$ ng/L; $P < .01$), but remained unchanged after placebo ($\Delta = +2 \pm 9$ ng/L; $P = $ NS). No significant correlation was found between FPG before the study or body weight and treatment effects on FPG or hormone levels.

Effect of MK-912 on B-Cell and A-Cell Function

Figure 5 shows the individual absolute differences between treatments of the AIR and C-peptide (ACR) response to an IV glucose load. The AIR to glucose was greater with MK-912 than placebo in eight of the 10 patients, an effect of borderline significance (43 ± 17 v 21 ± 10 pmol/L; $P = .06$). Similarly, the C-peptide response to glucose was greater with MK-912 than placebo in six of the eight patients in whom it was measured, but the difference did not reach statistical significance (0.07 ± 0.03 v 0.02 ± 0.02 nmol/L; $P = .07$).

The second-phase insulin response to glucose, measured as the area under the insulin curve from 10 to 60 minutes during the hyperglycemic clamp, was slightly greater with MK-912 compared with placebo, but this difference was not significant ($2,274 \pm 656$ v $1,889 \pm 433$ pmol/L over 50 minutes; $P = $ NS). The area under the C-peptide curve from 10 to 60 minutes was also not different between MK-912 and placebo (16 ± 4 vs 19 ± 5 nmol/L over 50 minutes; $P = $ NS) in the eight patients in whom it was measured.

During the hyperglycemic clamp (from 60 to 120 minutes), the increase in average plasma glucose from approximately 10 to 30 mmol/L caused an increase of plasma insulin with MK-912 (from 95 ± 8 to 181 ± 23 pmol/L) and placebo (from 83 ± 12 to 155 ± 18 pmol/L). The differences between MK-912 and placebo were not significant.

Figure 6 illustrates the individual absolute differences between treatments of the AIR, C-peptide (ACR), and glucagon (AGR) response to IV arginine during the hyperglycemic clamp. The AIR to arginine at this FPG level is maximal and estimates B-cell secretory capacity. The AIR was greater with MK-912 than placebo in eight of the 10 patients and there was a significant overall treatment effect (702 ± 96 v 604 ± 91; $P = .02$). In contrast, ACR to arginine was slightly greater with placebo than with MK-912, but the difference was not statistically significant (1.3 ± 0.1 v 1.4 ± 0.2 nmol/L; $P = $ NS). The AGR to arginine was greater with MK-912 than placebo in eight patients, and
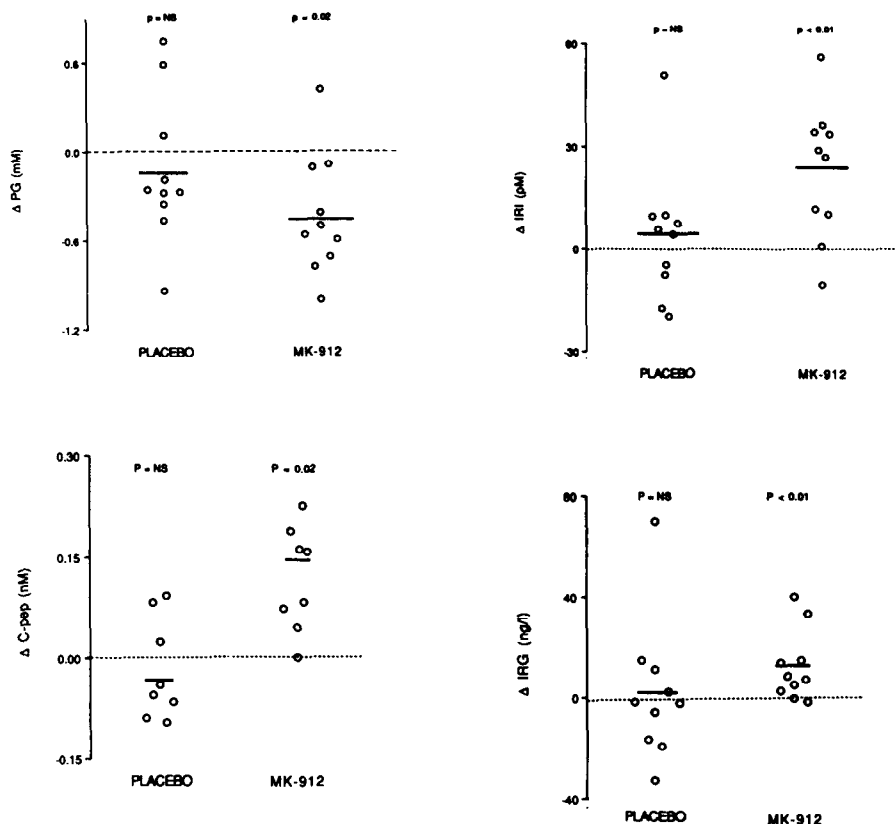
Fig 4. Absolute change from baseline, for each study subject, of fasting plasma glucose (PG), insulin (IRI), C-peptide (C-Pept), and glucagon (IRG) at 50 to 60 minutes after treatment. FPG decreased and hormone levels increased significantly after the administration of MK-912, but not after placebo (P values reflect within-treatment comparisons).

there was a significant overall treatment effect (116 ± 21 v 83 ± 21 ng/L; $P < .05$).

No significant correlation was found between FPG before the study or body weight and any of the parameters used to measure B- and A-cell function.

Adverse Effects

There were no clinically meaningful changes in hematology, blood chemistry, urinalysis, or EKG considered to be related to treatment with MK-912. One patient had a

vasovagal episode after dosing with MK-912 and shortly after micturition, which rapidly resolved without sequela. MK-912 appeared to be well tolerated by all subjects.

DISCUSSION

In the present study, we used a new orally active and selective α_2-blocker, MK-912, to determine whether increased α_2-adrenergic tone may be contributing to impaired B-cell function in NIDDM, and to evaluate the potential role of reducing α_2-adrenergic tone in the management of
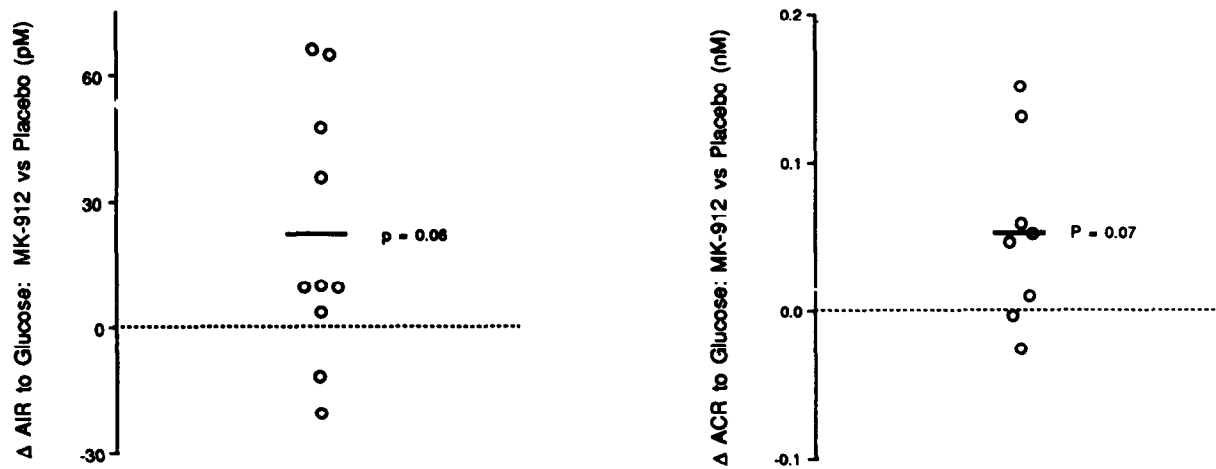

Fig 5. Absolute difference between MK-912 and placebo of each study subject for the acute insulin response (AIR) and acute C-peptide response (ACR) to glucose (1.66 mmol/kg IV). The AIR to glucose was greater with MK-912 than placebo in eight of the 10 subjects and the ACR to glucose in six of the eight subjects in whom it was measured, but the mean differences were of borderline significance ($P < .07$).
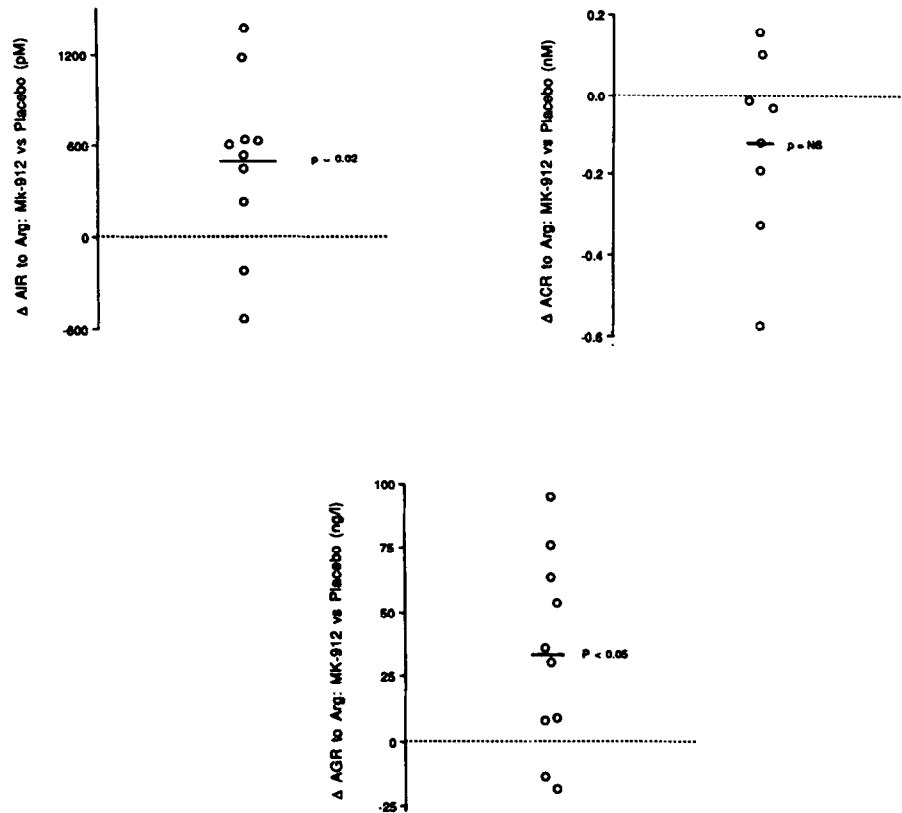
Fig 6. Absolute difference between MK-912 and placebo of each study subject for the acute insulin response (AIR), acute C-peptide response (ACR), and acute glucagon response (AGR) to arginine (5 g IV) during the hyperglycemic clamp. The AIR and AGR to arginine were greater in eight of the 10 subjects with MK-912 than placebo, but there was no treatment effect on the ACR to arginine.

NIDDM. Animal studies have shown that MK-912 reduced the FPG concentration and improved glucose tolerance in the insulin-resistant, hyperglycemic, ob/ob mouse model.[16]

The effectiveness of α_2-blockade following MK-912 is indicated by the consistent increase of plasma catecholamines and BP as observed with other α_2-antagonists in man.[17,18] The observations of the effects of MK-912 on plasma catecholamines in patients with NIDDM extend those made in normal volunteers[9] in which a mild pressor effect and an increase in plasma MHPG, an index of overall adrenergic function,[19] were demonstrated. These effects of MK-912 suggest central α_2-receptor antagonism.[10]

In the present study, we found a small increase in baseline plasma insulin with MK-912 that was associated with a small decrease in FPG. These results are consistent with recent studies with MK-912 in normal volunteers, as well as studies in which Midaglizole (Daiichi Pharmaceutical, Tokyo, Japan), a novel low-affinity α_2-adrenergic blocker, caused an increase in fasting plasma insulin and a modest decrease in FPG in normal subjects, and improved postprandial hyperglycemia in NIDDM.[20,21] However, in the latter studies, the specificity of Midaglizole as an α_2-adrenergic blocker was not demonstrated. Although the effectiveness of 2.0 mg MK-912 as an α_2-blocker has been demonstrated in previous studies using the α_2-agonist clonidine as a challenge,[10] we cannot rule out some other mechanism of action on glucose regulation.

Our finding of a slight improvement in AIR-max with MK-912 may suggest a small restoration of the maximal B-cell secretory capacity with α_2-blockade in NIDDM. This

is consistent with previous studies that showed a modest improvement of B-cell function in NIDDM with the nonspecific α-blocker phentolamine.[3,4] However, we cannot rule out the possibility that MK-912 may enhance B-cell function by a nonadrenergic mechanism, as suggested recently for phentolamine.[7] An additional mechanism to explain improved B-cell function with α_2-blockade would be an increase in synaptic NE release and a subsequent increased β-adrenergic effect on B cells leading to increased insulin secretion, as Broadstone et al have recently suggested.[4]

Compared with the significant treatment effect on the insulin response to arginine, the C-peptide response was not different between MK-912 and placebo. This apparent contradiction may be explained by differences in the kinetics of C-peptide compared with insulin. Changes of C-peptide levels do not reflect acute changes of insulin secretion, as well as plasma insulin levels.[22] The apparent contradiction might also be explained by an augmented secretion of proinsulin in response to MK-912, as proinsulin is not differentiated from true insulin by the immunoassay.[23]

The marginal effects of MK-912 on the first- and second-phase insulin responses to glucose are consistent with its modest effect on B-cell secretory capacity, and is also consistent with a recent study that failed to find any improvement in the first- and second-phase insulin responses to glucose with the specific α_2-blocker Idazoxan (Rackitt & Colman, Kingston upon Hull, UK) in a small number of patients with NIDDM.[24] An alternative explanation could be that the degree of hyperglycemia (>30 mmol/L) at which the second-phase insulin response was

measured may have overwhelmed an α_2-blocking effect that might have been more evident at lower plasma glucose levels.

The mild, but significant, enhanced A-cell function with MK-912 is particularly noteworthy in the presence of increased insulin levels, which would tend to suppress glucagon secretion.[25] This may suggest that the effect of the drug on A-cell function is not entirely the result of a primary effect on B-cell function.[26] These results are also in apparent discrepancy with the results observed with Mida-glizole,[20] although that study was conducted in normal subjects. The improvement in A-cell function with α_2-blockade may be explained by an increase in synaptic cleft NE secondary to presynaptic α_2-blockade, resulting in an accentuated β-adrenergic stimulation of A cells.

Other points merit discussion. First, it is possible that the degree of a patient's prior hyperglycemia or adiposity might influence endogenous α_2-adrenergic tone, and thereby the degree of effects of MK-912. We found no relationship between glucose control before the study or body weight and the positive effects of the α_2-adrenergic blocker MK-912 on FPG or B-cell function. However, due to the small sample size, the broad range of FPG (7 to 14 mmol/L), and the fact that our patients were "relatively" non-obese as compared with much of the NIDDM population, these findings must be interpreted with caution. Second, the significance of the small improvement in B-cell function with MK-912 cannot be fully assessed without a comparable study on age- and weight-matched normal subjects, which

was not done in the present study. Third, the increase of catecholamines and BP is of concern in patients with NIDDM. Any potentially useful therapeutic effect of an α_2-adrenergic blocker such as MK-912 on B-cell function of patients with NIDDM must be carefully weighed against these secondary changes.

In summary, in the present study, we have shown that in patients with NIDDM a single 2.0-mg oral dose of MK-912 causes (1) an effective α_2-blockade with increases in plasma catecholamines and BP; (2) a small increase of fasting plasma insulin levels, associated with a small decrease of FPG level; (3) a small improvement in B-cell function due to an increase in maximal B-cell secretory capacity; and (4) a small increase in basal and stimulated plasma glucagon concentrations. These findings suggest that endogenous α_2-adrenergic tone may contribute, although to a small extent, to the impaired B-cell function in NIDDM. If an α_2-blocker becomes available that does not increase BP, studies would be warranted to evaluate its potential impact on glucose regulation in patients with NIDDM.

ACKNOWLEDGMENT

REFERENCES

1. Kuhn CM, Cochrane C, Feinglos MN, et al: Exaggerated peripheral responsivity to catecholamines contributes to stress-induced hyperglycemia in the ob/ob mouse. Physiol Biochem Behav 26:491-495, 1987

2. Fujimoto K, Sakaguchi T, Ui M: Adrenergic mechanisms in the hyperglycemia and hyperinsulinemia of diabetic KK mice. Diabetologia 20:568-572, 1981

3. Robertson PR, Halter JB, Porte D: A role for α-adrenergic receptors in abnormal insulin secretion in diabetes mellitus. J Clin Invest 57:791-795, 1976

4. Broadstone VL, Pfeifer MA, Bajaj V, et al: α-Adrenergic blockade improves glucose-potentiated insulin secretion in non-insulin dependent diabetes mellitus. Diabetes 36:932-937, 1987

5. Langer J, Panton U, Zielman S: Effects of α-adrenoceptor antagonists on clonidine-induced inhibition of insulin secretion by isolated pancreatic islets. Br J Pharmacol 79:415-420, 1983

6. Angel I, Bidet S, Langer SZ: Pharmacological characterization of the hyperglycemia induced by α_2-adrenoceptor agonists. J Pharmacol Exp Ther 246:1098-1103, 1988

7. Ostenson C-G, Cattaneo AG, Doxey JC, et al: α-Adrenoceptors and insulin release from pancreatic islets of normal and diabetic rats. Am J Physiol 257:E439-E443, 1989

8. Pettibone DJ, Clineschmidt BV, Lotti VJ, et al: Pharmacologic profile of a new potent and specific α_2-adrenoceptor antagonist, L-657,743. Naunyn Schmiedebergs Arch Pharmacol 336:169-175, 1987

9. Gertz BJ, Vlassas PH, Rocci ML, et al: Clinical evaluation of a benzofuroquinolizine α_2-adrenoceptor antagonist. Clin Pharmacol Ther 46:566-575, 1989

10. Warren JB, Dollery CT, Fuller RW, et al: Assessment of

MK-912, an α_2-adrenoceptor antagonist, with use of intravenous clonidine. Clin Pharmacol Ther 46:103-109, 1989

11. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 28:1039-1057, 1979

12. Ward WK, Bolgiano DC, Mcknight B, et al: Diminished B-cell secretory capacity in patients with non-insulin dependent diabetes mellitus. J Clin Invest 74:1318-1328, 1984

13. Pek S, Fajans SS, Floyd JC, et al: Failure of sulfonylureas to suppress plasma glucagon in man. Diabetes 21:216-223, 1972

14. Evans MI, Halter JB, Porte D Jr: Comparison of double and simple enzymatic methods for measurement of catecholamines in human plasma. Clin Chem 24:567-570, 1978

15. Grizzle JE: The two-period change over design and its use in clinical trials. Biometrics 21:467-480, 1965 (corrections, Biometrics 30:727, 1974)

16. Saperstein R, Chapin EW, Brady E, et al: The effects of a potent, selective α_2 adrenoceptor antagonist, on glucose, and insulin levels in the ob/ob mouse. Diabetes 36:58A, 1987 (suppl)

17. Chaney DS, Heninger GR, Sternberg DE: Assessment of α_2-adrenergic autoreceptor function in humans; effects of oral yohimbine. Life Sci 30:2033-2041, 1982

18. Elliott HC, Jones CR, Vincent J, et al: The α-adrenoceptor antagonist properties of idazoxan in normal subjects. Clin Pharmacol Ther 36:190-196, 1984

19. Kopin IJ, Blomberg P, Ebert MH, et al: Disposition and metabolism of MHPG-CS$_3$ in humans: Plasma MHPG as the principal pathway of norepinephrine metabolism and as an important determinant of CSF levels of MHPG. Adv Biochem Psychopharmacol 39:57-68, 1984

20. Kawazu S, Suzuki M, Negishi K, et al: Studies of Midaglizole (DG-5128). A new type of oral hypoglycemic drug in healthy subjects. Diabetes 36:216-220, 1987

21. Kashiwagi A, Harano Y, Suzuki M, et al: New α_2-adrenergic blocker (DG-5128) improves insulin secretion and in vivo glucose disposal in NIDDM patients. Diabetes 35:1085-1089, 1986

22. Shapiro ET, Tillil H, Rubenstein AH, et al: Peripheral insulin parallels changes in insulin secretion more closely than C-peptide after bolus intravenous glucose administration. J Clin Endocrinol Metab 67:1094-1099, 1988

23. Ward WK, Paquette TL, Frank BH, et al: A sensitive radioimmunoassay for human proinsulin, with sequential use of anti-C-peptide and anti-insulin antisera. Clin Chem 32:728-733, 1986

24. Ostenson CG, Pigon J, Doxey JC, et al: α_2-Adrenoceptor blockade does not enhance glucose-induced insulin release in normal subjects or patients with noninsulin-dependent diabetes. J Clin Endocrinol Metab 67:1054-1059, 1988

25. Samols E, Tyler J, Marks V: Glucagon-insulin interrelationships, in Lefebvre PJ (ed): Glucagon: Glucagon: Molecular Physiology, Clinical and Therapeutic Implications. Oxford, UK, Pergamon, 1972, pp 151-173

26. Samols E, Stagner JI, Ewart RBL, et al: The order of microvascular cellular perfusion is B-A-D in the perfused rat pancreas. J Clin Invest 82:350-353, 1988