Nicotinic Acid as Therapy for Dyslipidemia in Non–Insulin-Dependent Diabetes Mellitus

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Recently, nicotinic acid has been recommended as a first-line hypolipidemic drug. To determine the effectiveness of nicotinic acid in dyslipidemic patients with non–insulin-dependent diabetes mellitus, 13 patients were treated in a randomized crossover trial. Patients received either nicotinic acid (1.5 g three times daily) or no therapy (control period) for 8 weeks each. Compared with the control period, nicotinic acid therapy reduced the plasma total cholesterol level by 24%, plasma triglyceride level by 45%, very-low-density lipoprotein cholesterol level by 58%, and low-density lipoprotein cholesterol level by 15%, and it increased the high-density lipoprotein cholesterol level by 34%. However, nicotinic acid therapy resulted in the deterioration of glycemic control, as evidenced by a 16% increase in mean plasma glucose concentrations, a 21% increase in glycosylated hemoglobin levels, and the induction of marked glycosuria in some patients. Furthermore, a consistent increase in plasma uric acid levels was observed. Therefore, despite improvement in lipid and lipoprotein concentrations, because of worsening hyperglycemia and the development of hyperuricemia, nicotinic acid must be used with caution in patients with non–insulin-dependent diabetes mellitus with dyslipidemia. We suggest that the drug not be used as a first-line hypolipidemic drug in patients with non–insulin-dependent diabetes mellitus.

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DYSLIPIDEMIA is a common finding in non–insulin-dependent diabetes mellitus (NIDDM)[1] and probably contributes causally to coronary heart disease, a major cause of death in patients with NIDDM.[2] Recently, the National Cholesterol Education Program proposed new guidelines for the management of high blood cholesterol levels.[3] The guidelines obviously could not consider in depth every subgroup of patients with hyperlipidemias, and, therefore, problems of management of lipid and lipoprotein abnormalities in patients with NIDDM were not addressed in detail. The National Cholesterol Education Program recommended nicotinic acid and bile acid binding resins as first-line drugs for treatment of hypercholesterolemia, and nicotinic acid was designated as the drug of choice for hypercholesterolemic patients with concurrent hypertriglyceridemia. Since hypertriglyceridemia is the most prevalent lipid abnormality in NIDDM, the guidelines could be interpreted to mean that nicotinic acid is the drug of choice for diabetic dyslipidemia. Patients with NIDDM, however, have other metabolic abnormalities, and, therefore, the choice of hypolipidemic drug may not be the same as in nondiabetic patients. The purpose of this study was to examine the potential usefulness of nicotinic acid for the treatment of dyslipidemia in patients with NIDDM.

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PATIENTS AND METHODS

Patients

Thirteen male patients with NIDDM from a lipid clinic and a diabetes clinic were studied at the Veterans Administration Medical Center, Dallas, Tex. All patients had an insidious onset of diabetes after age 38 years, and none had a history of ketosis. Their ages ranged from 49 to 68 years (mean ± SEM, 59 ± 1 years). Body weights and body-mass indexes averaged 91.7 ± 3.3 kg and 29.9 ± 0.7 kg/m^2, respectively. Four patients were receiving glyburide therapy, eight patients were receiving a combination of isophane insulin suspension and regular human insulin (Squibb-Novo, Princeton, NJ) subcutaneously before breakfast and supper for glycemic control, and one patient was receiving dietary therapy only. C-peptide levels were determined for patients receiving insulin therapy, both in the fasting state and 90 minutes after they ingested 480 mL of Sustacal (Mead Johnson & Co, Evansville, Ind); average values were 751 ± 182 and 1388 ± 192 pmol/L, respectively, confirming the diagnosis of NIDDM.[4] At entry, all patients had a plasma cholesterol level of 5.2 mmol/L or greater and/or a plasma triglyceride level of 2.8 mmol/L or greater. Six patients had coronary heart disease but none had recent myocardial infarction, unstable angina pectoris, or congestive heart failure. Patients were excluded if they had a history of peptic ulcer or gout, evidence of hyperuricemia (plasma uric acid concentration >475 μmol/L), or abnormal test results for liver, kidney, or thyroid gland functions. For patients taking specific hypolipidemic drugs, such therapy was discontinued at least 2 months prior to the study.

Experimental Design

The study protocol was approved by the institutional review board, and each patient gave informed consent. All patients were studied during three hospitalizations in the metabolic ward, each lasting 5 days. Before being randomized, patients were hospitalized for 5 days, called the baseline period, during which the dosage of insulin or glyburide was adjusted to achieve good glycemic control, and energy intake was determined to project a constant body weight. Thereafter, no changes in the dosage of insulin or glyburide were allowed except to prevent symptomatic hypoglycemia. The plasma glucose con-

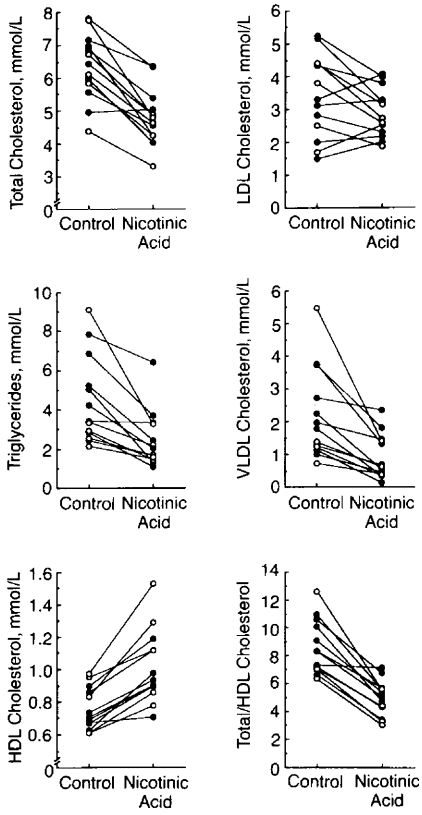

Fig 1.—Plasma levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, very-low-density lipoprotein (VLDL) cholesterol, and high-density lipoprotein (HDL) cholesterol and the ratio of total to HDL cholesterol during the control and the nicotinic acid periods in 13 patients with non–insulin-dependent diabetes mellitus with dyslipidemia. Each circle represents the mean of five daily determinations. Solid circles indicate mean values in patients receiving insulin therapy; open circles, values in patients receiving glyburide therapy or diet alone.

centration was measured at 3, 7, and 11 AM and 4 and 9 PM each day. Fasting blood samples were drawn daily for analysis of lipids and lipoproteins. Blood was also drawn for a glycosylated hemoglobin determination and a routine hematologic and chemistry profile, including the uric acid concentration. Patients were instructed to follow an isocaloric diet throughout the study, the diet containing 50% carbohydrates, 30% fat, and 20% protein, with 300 mg of cholesterol.[5] They were instructed not to consume alcohol during the trial.

After the baseline hospitalization, patients were randomized to receive nicotinic acid or no therapy for a period of 8 weeks. All patients then crossed over to the drug/no therapy (control) period for the next 8 weeks. A double-blind, placebo-controlled trial was not planned because of previous reports of the ineffective nature of this design due to symptomatic side effects of nicotinic acid therapy.[6] The nicotinic acid dosage was gradually increased from 50 mg three times daily on the first day to 1.5 g three times per day by the end of third week. Thereafter, patients continued to take the full dosage for the next 5 weeks. Patients reported as outpatients at two weekly intervals for a chemistry profile. On day 51 of each period, the patients entered the metabolic ward for 5 days, and blood samples were obtained each day as described above. On the last day of each period, plasma specimens were obtained every 2 hours for the determination of glucose levels. The patients were also interviewed about the side effects of the medication, such as flushing, rash, gastrointestinal distress, allergic reactions, and gout.

Table 1.—Effect of Nicotinic Acid Therapy on Plasma Lipid and Lipoprotein Levels*

	Study Period			
	Baseline	Control	Nicotinic Acid	P†
Plasma cholesterol, mmol/L	6.71±0.33	6.35±0.28	4.82±0.29	.0001
Plasma triglycerides, mmol/L	5.08±0.64	4.46±0.62	2.45±0.40	.0006
VLDL cholesterol, mmol/L	2.57±0.40	2.19±0.38	0.91±0.19	.0009
LDL cholesterol, mmol/L	3.39±0.42	3.40±0.35	2.89±0.21	.07
HDL cholesterol, mmol/L	0.76±0.05	0.76±0.04	1.02±0.06	.0001
Total cholesterol/HDL cholesterol	9.22±0.61	8.58±0.55	4.93±0.35	.0001

*VLDL indicates very-low-density lipoprotein; LDL, low-density lipoprotein; and HDL, high-density lipoprotein. Values are mean ± SEM. To convert values from millimoles per liter to milligrams per deciliter, multiply the cholesterol values by 38.67 and the triglyceride values by 88.574.
†Comparison between the control and nicotinic acid periods by a two-tailed paired *t* test.

Biochemical Analyses

Fasting plasma samples were analyzed for total cholesterol, triglyceride, and lipoprotein cholesterol concentrations according to Lipid Research Clinic procedures,[7] except that cholesterol and triglyceride concentrations were measured enzymatically.[8,9] Briefly, very-low-density lipoprotein (VLDL, density <1.006 kg/L) was removed by preparative ultracentrifugation, and the cholesterol level was measured in the VLDL subfraction and the infranatant. The high-density lipoprotein (HDL) cholesterol level was measured in the supernatant after lipoproteins containing apolipoprotein B were precipitated by heparin-manganese.[7] Cholesterol in the low-density lipoprotein (LDL) fraction was taken as the difference between the cholesterol content of the 1.006-kg/L infranatant and HDL cholesterol.

The plasma glucose concentration was determined by glucose oxidase method using a glucose analyzer (Beckman Instruments Inc, Fullerton, Calif). Quantitative analysis of glycosylated hemoglobin was done by agar gel electrophoresis using kits (Helena Laboratories, Beaumont, Tex). The plasma C-peptide concentration was measured by radioimmunoassay kits (Mallinckrodt Inc, St Louis, Mo).

Statistical Analyses

A repeated-measures analysis of variance test was performed to compare the baseline, nicotinic acid, and control periods, to assess the effect of the sequence in which the patients were assigned to the control or active drug period, and to assess differences in response between patients receiving insulin and other therapy.[10,11] Multiple comparisons were made with use of the two-tailed paired *t* test with Bonferroni's correction. When three periods were included in the analysis, $P<.0167$ was considered significant. The Wilcoxon signed rank test was used for data not consistent with the hypothesis of normality. The areas under the curve were compared with use of a *t* test. All results are expressed as mean ± SEM.

RESULTS

The analysis of variance did not reveal any differences in the response to nicotinic acid therapy whether patients received insulin, glyburide, or no hypoglycemic drugs; therefore, plasma lipid and lipoprotein values in all patients were pooled. Results for each patient are shown in Fig 1, and results for all patients are summarized in Table 1. The order in which patients were allocated to the drug and control periods had no effect on the results. Plasma lipid and lipoprotein concentrations were not significantly different in the baseline and control periods (Table 1).

Compared with the control period, nicotinic acid therapy reduced the plasma total cholesterol level by 24%. Plasma triglyceride levels were reduced by 45% ($P<.001$) and VLDL cholesterol levels by 58% ($P<.001$). The LDL cholesterol levels showed a modest 15% decrease with nicotinic acid therapy, which approached statistical significance ($P=.07$). The HDL cholesterol concentrations rose consistently, with

Table 2.—Metabolic Variables During the Study*

	Study Period			
	Baseline	Control	Nicotinic Acid	P†
Mean plasma glucose, mmol/L‡	7.19±0.31	7.85±0.50	9.09±0.63	.068
24-h plasma glucose profile, mmol·h/L§	...	194.1±6.2	213.5±7.4	.047
Insulin dosage (n=8), U/d	85.4±9.5	87.4±10.0	91.5±10.2	.50
Glyburide dosage (n=4), mg/d	6.25±3.0	2.50±1.0	6.25±3.0	1.0
Glycosylated hemoglobin, %	9.6±0.4	8.7±0.6	10.5±0.5	.002
24-h urinary glucose, g/d	3.1±1.3	3.6±1.4	14.9±6.3	.016
Plasma uric acid, μmol/L‖	398±22	382±22	511±33	.0001
Body weight, kg	91.7±3.3	92.1±2.8	91.1±2.8	.19

*Values are mean±SEM.
†Comparison between the control and nicotinic acid periods by a two-tailed paired *t* test.
‡Plasma glucose values were determined at 3, 7, and 11 AM and 4 and 9 PM for 5 days during hospitalization. To convert values from millimoles per liter to milligrams per deciliter, multiply by 18.02.
§Plasma glucose values were determined at 2-hour intervals for 24 hours on the last day of hospitalization in nine patients. Values are given in area-under-the-curve units.
‖To convert plasma uric acid values from micromoles per liter to milligrams per deciliter, multiply by 0.0168.

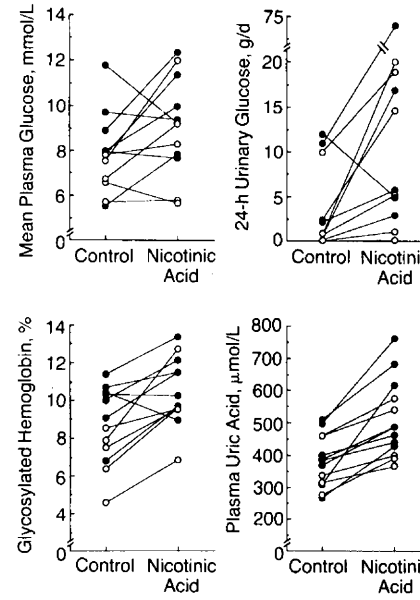

Fig 2.—Mean plasma glucose, 24-hour urinary glucose, glycosylated hemoglobin, and plasma uric acid levels during the control and the nicotinic acid periods in 13 patients with non–insulin-dependent diabetes mellitus with dyslipidemia. Solid circles indicate mean values in patients receiving insulin therapy; open circles, values in patients receiving glyburide therapy or diet alone.

an average increase of 34% ($P<.0001$). The ratio of total cholesterol to HDL cholesterol also improved strikingly during nicotinic acid therapy.

The daily requirements of hypoglycemic drugs did not change in 10 of 13 patients. In one patient, due to mild hypoglycemic episodes in the control period, the daily insulin dosage was reduced by 4 U. In another patient, glyburide therapy was discontinued due to persistently low blood glucose levels reported on self-monitoring during the control period. In the third patient, nicotinic acid therapy caused an unanticipated marked deterioration in fasting plasma glucose values (from an average of 8.2 mmol/L during the control period to 18.2 and 21.5 mmol/L during the outpatient follow-up with nicotinic acid therapy), necessitating an increase in the daily insulin dosage from 76 to 105 U. Despite a 38% increase in the daily insulin dosage, the patient's mean plasma glucose values during hospitalization remained elevated (11.3 mmol/L) during nicotinic acid therapy compared with values during the control period (7.8 mmol/L). Although the increase in insulin dosage in this patient did not follow the original protocol, he was not excluded from analysis.

Overall, glycemic control deteriorated during nicotinic acid therapy, as evidenced by a 16% increase in mean plasma glucose levels, from 7.8 to 9.1 mmol/L. Concentrations of glycosylated hemoglobin increased by 21% during nicotinic acid therapy, and marked glycosuria was noted in some patients (Table 2 and Fig 2). A daylong profile of plasma glucose, obtained on the last day of each period in nine patients, also revealed significantly higher values during nicotinic acid therapy (Table 2).

Nicotinic acid therapy increased plasma uric acid levels in all the patients (Table 2 and Fig 2). No patient, however, suffered from acute gouty arthritis. In two patients, mean plasma uric acid values rose to extremely high levels—684 and 761 μmol/L—with nicotinic acid therapy (Fig 2). Both of these patients had borderline low values of creatinine clearance, 1.05 and 1.08 mL/s, respectively, at entry into the study. A slight increase in the plasma creatinine concentration and a reduction in creatinine clearance was also noted in both patients during nicotinic acid therapy. No changes in the plasma creatinine concentration or creatinine clearance were noted in any other patients.

Most patients tolerated nicotinic acid therapy well except for minor complaints of flushing. None developed significant abnormalities in hepatic function test results throughout the study. One patient reported headaches but also noted improvement in claudication distance during nicotinic acid therapy. No patient dropped out as a consequence of side effects.

COMMENT

Soon after the discovery of the plasma lipid-lowering potential of nicotinic acid therapy by Altschul et al,[12] deterioration of glucose tolerance with this agent was reported in both nondiabetic subjects[13-16] and patients with NIDDM.[13,17] Since most of these claims were anecdotal, the potential clinical significance of this side effect has not been given due consideration. For instance, recent guidelines of the National Cholesterol Education Program can be taken to indicate that nicotinic acid is the drug of choice for treatment of dyslipidemia associated with NIDDM.[3] The current investigation, therefore, was carried out to examine carefully whether nicotinic acid will favorably modify plasma lipid and lipoprotein concentrations in patients with NIDDM without significantly worsening their glycemic control.

In our patients, nicotinic acid therapy was highly effective for lowering levels of plasma triglycerides and VLDL cholesterol. It also raised levels of HDL cholesterol, with an increase averaging 34%. Total cholesterol levels were reduced significantly, as were total/HDL cholesterol ratios. Nicotinic acid therapy reduced LDL cholesterol levels in most but not all patients. Still, it generally *did not* produce the rise in LDL cholesterol concentrations commonly observed with other triglyceride-lowering therapies, eg, fibric acids[18,19] or n-3 polyunsaturated fatty acids.[20,21]

This study leaves little doubt that nicotinic acid therapy improves the lipoprotein profile in patients with NIDDM. On the other hand, the drug also causes a deterioration in glycemic control. In almost all patients, levels of glycosylated hemoglobin rose with nicotinic acid therapy. The daily profile of plasma glucose during hospitalization revealed an overall 16% elevation in mean plasma glucose levels during the nicotinic acid period. Finally, treatment with nicotinic acid induced marked glycosuria in some patients. Two-hourly profiles of plasma glucose on the last day of hospitalization also revealed elevated plasma glucose values during nicotinic

acid therapy. Therefore, it can be argued that the benefits of improving lipoprotein values during administration of nicotinic acid to patients with NIDDM may be counterbalanced by worsening hyperglycemia.

The results of our study suggest that a number of patients whose hyperglycemia is well controlled by dietary therapy alone may need to take hypoglycemic agents during nicotinic acid treatment. In others, the dosage of insulin or oral hypoglycemic drugs may have to be increased to control nicotinic acid–induced hyperglycemia. There are theoretical objections to increasing the insulin dosage for correction of metabolic derangements caused by another agent. For example, marked hyperinsulinemia may have a direct role in atherogenesis.[22] Furthermore, modest increases in insulin dosage may not be able to correct nicotinic acid–induced hyperglycemia, as was observed in one of the patients. Thus, it cannot be assumed that the worsening of hyperglycemia with nicotinic acid can be easily corrected by increasing the dosage of insulin or oral hypoglycemic drugs. Since the hyperglycemic action of nicotinic acid may be dose-dependent, some may argue that the dosage of nicotinic acid can be reduced if glycemic control deteriorates. However, the improvement in the lipoprotein profile likewise may not be optimal.

The mechanism for the hyperglycemic action of nicotinic acid in patients with NIDDM is not clear. Recently, it has been reported that nicotinic acid therapy may induce insulin resistance in normal, healthy volunteers.[23] The same could be true for patients with NIDDM. Whether nicotinic acid has any adverse effects on beta-cell function is not known, but there is no evidence to support such an action.[15,23] Another possibility is that, by interfering with triglyceride synthesis in the liver, nicotinic acid may enhance utilization of fatty acids at the expense of glucose; if so, this could lead to enhanced hepatic glucose output, another potential cause of hyperglycemia.

Another adverse effect of nicotinic acid therapy in this study was a consistent increase in plasma uric acid levels. Long-term therapy with nicotinic acid is known to increase the occurrence of acute gouty arthritis and to require greater usage of antigout medication.[24] Since patients with impaired glucose tolerance and NIDDM may be predisposed to develop hyperuricemia and gout,[25,26] nicotinic acid therapy may further increase the risk for development of gout. Although not all investigators agree that asymptomatic hyperuricemia is nephrotoxic, increases in plasma uric acid levels may not be benign in patients with NIDDM who are predisposed to diabetic nephropathy. Indeed, in two of our patients, marked hyperuricemia caused by nicotinic acid therapy further compromised their renal function.

To summarize, nicotinic acid therapy markedly improves the lipoprotein profile of patients with NIDDM. Although nicotinic acid generally was well tolerated in the current patients, it is known to have a variety of side effects that preclude its use in many patients. For patients with NIDDM in particular, two side effects emerge as especially worrisome. First, the drug causes deterioration of glucose control, which, for long-term therapy, must be considered a definite drawback. Also, nicotinic acid raises uric acid levels, which increases the risk for gout and could have a negative effect on renal function. For most patients with NIDDM who have dyslipidemia, therefore, nicotinic acid therapy must be used with caution, although it may be useful in primary forms of dyslipidemia. On the basis of our previous studies, we suggest that a hydroxymethylglutaryl coenzyme A reductase inhibitor[27] or, for marked hypertriglyceridemia, a fibric acid derivative[19] may be preferable as a lipid-lowering drug. Further studies, however, are needed to identify the optimal pharmacologic approach to lipid lowering in patients with NIDDM.[28]

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