Long-Term Effects of a Sustained-Release Preparation of Acipimox on Dyslipidemia and Glucose Metabolism in Non–Insulin-Dependent Diabetes Mellitus

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Elevated circulating plasma nonesterified fatty acids (NEFA) may contribute to the insulin resistance and hyperglycemia of non–insulin-dependent diabetes mellitus (NIDDM), and decreasing plasma NEFA could provide a therapeutic benefit. A sustained-release preparation of acipimox, a lipolysis inhibitor, was used in an attempt to decrease circulating plasma NEFA levels long-term, and the effects on glycemic control, insulin resistance, and serum lipids were measured. Sixty NIDDM patients (43 males and 17 females) took part in a randomized controlled trial of acipimox or placebo for 12 weeks. Fasting plasma NEFA levels did not change in acipimox-treated patients (baseline *v* 12 weeks, 0.84 ± 0.35 *v* 0.88 ± 0.55 mmol · L^{-1}, mean ± SD). Fasting blood glucose was unchanged (mean difference *v* placebo, −0.5 mmol · L^{-1}; 95% confidence interval [CI], −1.4 to 0.3 mmol · L^{-1}), but serum fructosamine decreased (mean difference *v* placebo, −26 μmol · L^{-1}; 95% CI, −51 to 0 mmol · L^{-1}), as did the standardized hemoglobin A_1 ([HbA_1] mean difference *v* placebo, −1.4%; 95% CI, −3.0% to −0.1%). Insulin resistance measured as steady-state plasma glucose during an insulin-dextrose infusion test was unchanged (mean difference *v* placebo, −1.4 mmol · L^{-1}; 95% CI, −3.2 to 0.5 mmol · L^{-1}). Serum total cholesterol (mean difference *v* placebo, −0.4 mmol · L^{-1}; 95% CI, −0.6 to −0.1 mmol · L^{-1}), serum apolipoprotein B ([apo B] mean difference *v* placebo, −0.19 g · L^{-1}; 95% CI, −0.3 to −0.1 g · L^{-1}), and serum triglycerides (mean difference *v* placebo for pretreatment *v* posttreatment ratio, 0.59; 95% CI, 0.40 to 0.88) were all lower with acipimox. Serum high-density lipoprotein (HDL) cholesterol (mean difference *v* placebo, 0.10 mmol · L^{-1}; 95% CI, −0.05 to 0.3 mmol · L^{-1}), serum apo A1 (mean difference *v* placebo, 0.03 g · L^{-1}; 95% CI, −0.04 to 0.1 g · L^{-1}), and serum lipoprotein(a) ([Lp(a)] acipimox *v* placebo, 154 (0 to 1,574) *v* 71 (0 to 1,009), median and range) were unchanged. Despite the lack of change in fasting plasma NEFA levels, acipimox caused a modest beneficial improvement in overall glycemic control and plasma lipids in NIDDM patients and could be a useful agent in the treatment of dyslipidemic NIDDM patients.

HYPERGLYCEMIA is the pathognomic biochemical abnormality of non–insulin-dependent diabetes mellitus (NIDDM), but other metabolic disturbances such as hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, and reduced insulin sensitivity are also common. Increased circulating nonesterified fatty acids (NEFA) are also characteristic of the condition[1] and may contribute to these abnormalities.

In 1963, Randle proposed the glucose–fatty acid cycle on the basis of in vitro experiments in rat heart and diaphragm preparations demonstrating impaired glucose oxidation and increasing lipid oxidation rates in response to increasing NEFA.[2] In human in vivo experiments, NEFA have been shown to impair glucose uptake by both cardiac and skeletal muscle.[3] Investigations in both diabetic and nondiabetic subjects have demonstrated that acute increases in circulating plasma NEFA impair glucose oxidation,[4] increase lipid oxidation,[4] reduce whole-body glucose disposal,[4-6] and sometimes result in excess hepatic glucose output (HGO).[5-8] Acutely decreasing plasma NEFA levels in NIDDM subjects increases carbohydrate oxidation and correspondingly reduces lipid oxidation,[9-12] and whole-body glucose disposal is increased.[9-11] In some short-term studies, fasting blood glucose was found to be lower[13,14] and HGO was reduced,[10] but this is not a consistent finding.[11,15]

Attempts at a sustained decrease of plasma NEFA have not translated into long-term improvement in blood glucose control in NIDDM subjects. Nicotinic acid, a potent lipolysis inhibitor that decreases plasma NEFA, in fact worsens blood glucose control.[16,17] This anomaly is probably explained by the rebound in NEFA levels that occurs 2 to 3 hours after drug administration.[18] Acipimox, a nicotinic acid analog, has a similar but more sustained effect on plasma NEFA levels without the same degree of rebound,[18] but in long-term studies does not appear to improve blood glucose control.[19-21] However, in these studies, adequate suppression of plasma NEFA levels was not demonstrated,[19] and a rebound increase in NEFA levels has been reported.[20]

However, sustained suppression of plasma NEFA levels could lead to improvements in insulin sensitivity and glycemic control. A sustained-release preparation of acipimox has been shown to decrease plasma NEFA over 24 hours in NIDDM subjects.[13] Acipimox is an attractive agent because it also decreases total cholesterol and triglycerides in NIDDM subjects.[19,21,22] Acipimox,[23] like nicotinic acid,[23,24] has also been shown to decrease elevated lipoprotein(a) [Lp(a)] levels in nondiabetic subjects, an effect that may have further benefits on decreasing the coronary risk. We have therefore used this preparation in a long-term trial to assess its effect on the insulin sensitivity, glycemic control, and lipid profile in NIDDM subjects.

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SUBJECTS AND METHODS

Patients

Sixty NIDDM subjects attending outpatient diabetes clinics in Newcastle upon Tyne, UK, Middlesbrough, UK, and Dusseldorf, Germany, took part in the study. All provided written informed consent, and the study was approved by the local ethics committees. All subjects were otherwise in good health without significant cardiac, renal, or hepatic disease. No subject was on biguanides or lipid-lowering therapy during the course of the study or in the 3 months before entry to the study. Subjects on sulfonylurea treatment continued as usual during the study. Subjects who were on other medications, including beta-blockers and thiazide diuretics, for at least 3 months before entry to the study were allowed to continue on the medications during the study. All subjects received advice on a prudent diabetic diet and were advised to continue with it throughout the study. The study was designed to show a difference of 1.0 mmol $\cdot$ L^{-1} in the change in fasting plasma glucose between acipimox and placebo. To achieve 80% power with a significance level of 5%, it was estimated that 56 patients should be randomized to the study (a standard deviation of 1.3 was based on unpublished data, G. Fulcher, 1989). Analysis was made on an intention-to-treat basis. Acipimox and placebo preparations were supplied by Farmitalia Carlo Erba (Milan, Italy) and were stored and dispensed according to a predetermined randomization schedule by the local hospital pharmacies.

Study Protocol

The study was conducted as a double-blind placebo-controlled trial. After a 4-week run-in period to confirm stable blood glucose control and dyslipidemia, subjects were randomized to receive either placebo or acipimox 500 mg on rising and at bedtime. The treatment period was 12 weeks, and subjects were evaluated halfway through the treatment period and on completion. Fasting blood samples were obtained to measure blood glucose, serum insulin, C-peptide, cholesterol, triglycerides, HDL cholesterol, apolipoprotein A1 (apo A1), apo B, Lp(a), fructosamine, plasma NEFA, and hemoglobin A_1 (HbA_1) or HbA_{1c} levels. Just before commencement of the treatment period and at the end of the treatment period, each subject underwent a meal tolerance test (MTT) and an insulin sensitivity test on separate days. For the MTT, each subject presented in the fasting state at 8 AM, a cannula was placed in a forearm vein for blood sampling, and after 20 minutes of rest, a fasting blood sample was collected. Each subject then consumed a standard breakfast (500 kcal, approximately 50% carbohydrate, 35% fat, and 15% protein), and blood samples were taken every 15 minutes for 60 minutes and thereafter every 30 minutes for a further 90 minutes to measure blood glucose and intermediary metabolites, serum insulin and C-peptide, and plasma NEFA levels. For the insulin sensitivity test, subjects again presented fasting at 8 AM. An intravenous cannula was placed in an antecubital vein for infusions. In the contralateral arm, a cannula was placed retrogradely in a dorsal hand vein, and the hand was placed in a thermoregulated Plexiglas box with temperature maintained at 55°C for arterialized blood sampling. After 20 minutes' rest, basal samples were collected and simultaneous infusions of glucose (6 mg $\cdot$ kg^{-1} $\cdot$ min^{-1}) and insulin (Human Actrapid 100 U $\cdot$ mL^{-1}; Novo-Nordisk, Copenhagen, Denmark) (0.05 U $\cdot$ kg^{-1} $\cdot$ h^{-1}) were commenced. From 120 to 150 minutes after starting the infusions, blood was sampled at 10-minute intervals for measurement of blood glucose and glycerol, serum insulin, C-peptide, and triglyceride, and plasma NEFA levels. Results were averaged to derive steady-state concentrations. This method of assessing insulin sensitivity has been well correlated with results from euglycemic-hyperinsulinemic clamp studies.[25,26] Acipimox or placebo were administered once basal samples were collected on the days of the MTT and insulin sensitivity tests. Subjects were asked to report all possible adverse events, and the full blood cell count, electrolyte, urea, creatinine, calcium, and phosphate levels, and liver function were measured at the beginning and end of the study.

Analytical Procedures

Assays were performed in Newcastle upon Tyne, except for serum insulin and C-peptide, which were assayed in Dusseldorf. Samples for plasma glucose, serum insulin, C-peptide, cholesterol, triglyceride, HDL cholesterol, and fructosamine were stored at −40°C, and samples for plasma NEFA and serum apo A1, apo B, and Lp(a) were stored at −70°C. Samples were stored for up to 6 months. Plasma glucose was determined by the glucose oxidase method using a YSI glucose analyzer (Yellow Springs Instruments, Yellow Springs, OH; interassay coefficient of variation [CV], 2.9% at 13.1 mmol $\cdot$ L^{-1} and 2.5% at 9.1 mmol $\cdot$ L^{-1}). The HbA_{1c} level was measured by an enzyme immunoassay (Dako Diagnostics, Ely, Cambridgeshire, UK; reference range, 2.8% to 4.4%). Plasma NEFA levels were measured by an enzymatic technique[27] using a Cobas Bio (Roche, Welwyn Garden City, UK) centrifugal analyzer (interassay CV, 2.7% at 0.22 mmol $\cdot$ L^{-1} and 2.0% at 0.64 mmol $\cdot$ L^{-1}). Blood 3-hydroxybutyrate was estimated in perchloric acid extracts of whole blood using enzymatic methods[28] with a Cobas Bio (Roche) automated enzymatic centrifugal analyzer (CV, 4.3%). Serum triglyceride levels were measured by the glycerol kinase method without correction for free glycerol using commercial kits (Roche; interassay CV, 2.8% at 2.1 mmol $\cdot$ L^{-1} and 3.9% at 4.7 mmol $\cdot$ L^{-1}). The cholesterol level was measured by the cholesterol oxidase method with BCL kits (Lewes, East Sussex, UK) with the Cobas Bio centrifugal fast analyzer (Roche; interassay CV, 2.0% at 3.8 mmol $\cdot$ L^{-1}, 1.9% at 7.5 mmol $\cdot$ L^{-1}, and 2.3% at 8.9 mmol $\cdot$ L^{-1}). HDL cholesterol was estimated after precipitation of apo B–containing lipoproteins with heparin and manganese (interassay CV, 8.2% at 1.0 mmol $\cdot$ L^{-1}). Insulin was estimated with a double-antibody radioimmunoassay (interassay CV, 10.7%; Pharmacia Diagnostics, Uppsala, Sweden). The C-peptide level was measured by radioimmunoassay (interassay CV, 8.6%; Diagnostik Systems Laboratories, Frankfurt, Germany). Serum apolipoprotein levels were measured by immunonephelometry using a Behring Laser Nephelometer (Marburg, Germany; interassay CV: apo A1, 6.0% at 1.0 mg $\cdot$ L^{-1}; apo B, 6.3% at 0.6 mg $\cdot$ L^{-1} and 8.3% at 1.1 mg $\cdot$ L^{-1}). Lp(a) was estimated by enzyme immunoassay (TintElize Lp(a); Biopod, Umea, Sweden).

Calculations and Statistical Methods

Results are presented as the mean ± SD or median (range). For each variable, the change from the baseline to the end of the study (12 weeks) was calculated. This was compared between treatments using an analysis of covariance adjusting for both center and baseline levels. Non–normally distributed variables were logarithmically transformed. For these variables, the ratio of the geometric mean of posttreatment to pretreatment results or difference in this ratio are presented, with a value of 1 representing no change. The HbA_1 assay was changed to a HbA_{1c} assay in Newcastle upon Tyne during the course of the study. All HbA_1 and HbA_{1c} values were standardized for comparison (51 of 60 subjects had assays by a single method only). To standardize the results, the lower end of the range (5.5 and 2.79 for HbA_1 and HbA_{1c}, respectively) was subtracted from each value and the resulting difference divided by the width of the range (2 and 0.86 for HbA_1 and HbA_{1c}, respectively).[29] This method has the effect of producing dimensionless values so that the values derived from the two assays can be used together. It also makes no assumptions about the way in which the ranges were derived nor about the underlying distribution of the data. The "standardized" HbA_1 data were then combined for analysis, and standardized results have been converted back to HbA_1 units for presentation. Lp(a) data were analyzed nonparametrically using a sign test. The area under the curve (AUC) for the insulin sensitivity test and MTT were calculated using the trapezoid rule. AUC and 2-hour values for blood glucose, serum insulin,

and plasma NEFA were highly correlated in a linear relationship ($r = .92$), and statistical analysis was therefore performed on 2-hour values only. For the insulin sensitivity test, steady-state values for the last 30 minutes of the test were analyzed.

RESULTS

Seventy-nine subjects entered the study, and 60 were randomized (Table 1). The 19 subjects who were not randomized failed to meet the criteria of stable lipid or glycemic control during the run-in period. Body weight remained constant throughout the study period in both the treatment and control groups (data not shown). A similar proportion of subjects used sulfonylureas in both centers. Patients studied in Newcastle upon Tyne and Middlesbrough were significantly older (62 ± 6 *v* 56 ± 8 years, $P = .001$) and leaner (body mass index [BMI], 27.2 ± 2.8 *v* 29.9 ± 2.9 kg · m^{-2}, $P = .002$) than subjects studied in Dusseldorf. Two subjects in the acipimox group and two in the placebo group failed to complete the study. One subject on acipimox suffered severe nausea and had to withdraw, and the other withdrew after falling and breaking ribs. One subject on placebo had increasing hyperglycemic symptoms and withdrew, and a further subject did not wish to complete the study.

Lipids

Values for plasma NEFA, serum total cholesterol, HDL cholesterol, triglycerides, apo A1, apo B, and Lp(a) at baseline and 6 and 12 weeks are shown in Table 2. Fasting plasma NEFA, although significantly higher after 12 weeks' treatment with acipimox versus placebo (mean difference, +0.24 mmol · L^{-1}; 95% CI, 0.02 to 0.46), did not change significantly from baseline in either group (placebo, 0.69 ± 0.24 *v* 0.56 ± 0.19 mmol · L^{-1}; acipimox, 0.84 ± 0.35 *v* 0.88 ± 0.55 mmol · L^{-1}). After acipimox, there were significant decreases compared with placebo in serum total cholesterol (mean difference, −0.4 mmol · L^{-1}; 95% CI, −0.6 to −0.1), serum triglycerides (mean difference in posttreatment to pretreatment ratio, 0.59; 95% CI, 0.40 to 0.88), and serum apo B (mean difference, −0.19 mg · L^{-1}; 95% CI, −0.3 to −0.1). Serum HDL cholesterol (mean difference, +0.10 mmol · L^{-1}; 95% CI, −0.05 to +0.30) and serum apo A1 (mean difference, +0.03 mg · L^{-1}; 95% CI, −0.04 to +0.10) did not change significantly between treatments. Acipimox had no significant effect on Lp(a) levels.

Glycemic Control

Values for fasting plasma glucose and serum fructosamine, insulin, and HbA_1 at baseline and 6 and 12 weeks are shown in Table 3. The change in fasting plasma glucose was not different between placebo and acipimox (mean difference, −0.5 mmol · L^{-1}; 95% CI, −1.4 to 0.3). Serum fructosamine was significantly lower in the treatment group (mean difference, −26 mmol · L^{-1}; 95% CI, −51 to 0). Standardized glycated hemoglobin was significantly lower in the acipimox group (mean difference, −1.4%; 95% CI, −3.0% to −0.1%). Fasting serum insulin and C-peptide values did not change during the study (insulin mean difference in posttreatment to pretreatment ratio, 1.17; 95% CI, 0.97 to 1.4; C-peptide mean difference in posttreatment to pretreatment ratio, 1.15; 95% CI, 0.93 to 1.41).

Table 1. Characteristics of 60 Subjects Randomized in the Study (mean ± SD)

Characteristic	Placebo	Acipimox
No. of subjects	31	29
Male/female ratio	21/10	22/7
UK/Germany	19/12	19/10
Sulfonylurea use	19	24
Age (yr)	59 ± 6	60 ± 8
BMI (kg · m^{-2})	29.0 ± 2.9	27.9 ± 3.0
Diabetes duration (yr)	6.0 ± 5.4	4.3 ± 3.0

Table 2. Fasting Plasma NEFA, Serum Total Cholesterol, HDL Cholesterol, Triglycerides, Apo A1, Apo B, and Lp(a) During 12 Weeks' Treatment With Placebo or Acipimox (mean ± SD or median and range)

Parameter	Baseline	6 Weeks	12 Weeks
NEFA (mmol · L^{-1})			
Placebo	0.69 ± 0.24	0.51 ± 0.22	0.56 ± 0.19*
Acipimox	0.84 ± 0.35	0.84 ± 0.61	0.88 ± 0.55
Total cholesterol (mmol · L^{-1})			
Placebo	5.6 ± 0.7	6.1 ± 0.8	5.6 ± 0.8*
Acipimox	5.6 ± 1.3	5.9 ± 1.3	5.3 ± 1.3
Triglycerides (mmol · L^{-1})			
Placebo	1.9 (0.6-3.3)	2.3 (0.6-7.9)	2.0 (0.6-4.1)*
Acipimox	2.4 (0.4-2.7)	1.9 (0.7-4.1)	1.7 (0.6-4.6)
HDL cholesterol (mmol · L^{-1})			
Placebo	1.1 ± 0.3	1.3 ± 0.4	1.0 ± 0.3
Acipimox	1.1 ± 0.3	1.2 ± 0.3	1.2 ± 0.4
Apo A1 (g · L^{-1})			
Placebo	1.1 ± 0.3	1.2 ± 0.3	1.1 ± 0.3
Acipimox	1.2 ± 0.3	1.3 ± 0.3	1.2 ± 0.3
Apo B (g · L^{-1})			
Placebo	1.0 ± 0.2	1.2 ± 0.3	1.1 ± 0.2*
Acipimox	1.2 ± 0.2	1.1 ± 0.2	1.0 ± 0.2
Lp(a) (mg · L^{-1})			
Placebo	80 (0-942)	82 (0-1,016)	71 (0-1,009)
Acipimox	116 (0-1,531)	140 (0-1,620)	154 (0-1,574)

*Statistically significant difference.

Table 3. Fasting Plasma Glucose and Serum Insulin, Fructosamine, and Glycated Hb After 12 Weeks' Treatment With Placebo or Acipimox (mean ± SD or median and range)

	Baseline	6 Weeks	12 Weeks
Glucose (mmol · L^{-1})			
Placebo	9.8 ± 2.9	9.8 ± 2.8	9.6 ± 2.6
Acipimox	10.8 ± 2.6	10.1 ± 2.8	10.1 ± 2.5
Insulin (mU · l^{-1})			
Placebo	10 (5-29)		11 (1-28)
Acipimox	14 (6-40)		14 (6-53)
Fructosamine (mmol · L^{-1})			
Placebo	352 ± 80	366 ± 79	338 ± 74*
Acipimox	339 ± 54	339 ± 61	314 ± 47
Glycated Hb (%)			
Placebo	10.7 ± 2.4	10.9 ± 2.6	12.3 ± 3.8*
Acipimox	10.9 ± 2.6	10.9 ± 3.0	10.5 ± 2.2

*Statistically significant difference.

Insulin Sensitivity

Table 4 shows the change in 2-hour plasma glucose and NEFA and serum insulin during the MTT and steady-state plasma glucose and NEFA and serum insulin during the insulin infusion test. Figure 1 shows the excursion of plasma glucose, serum insulin, and plasma NEFA before and after treatment with placebo or acipimox during the MTT. After 12 weeks of treatment, there were no demonstrable differences in these indices of insulin sensitivity. The combined data show a lower 2-hour glucose and higher 2-hour NEFA after acipimox during the MTT, but for these variables and steady-state plasma NEFA during the insulin infusion test, there was evidence of an interaction between treatment and center, and separate results for each center may be more meaningful.

Between-Center Differences

For variables where there was a difference between centers for the changes between placebo and acipimox, the differences are shown in Table 5. There was no relationship demonstrated between the change in fasting plasma glucose or serum fructosamine and the change (absolute or percent) in fasting plasma NEFA, 2-hour plasma NEFA during the MTT, or steady-state plasma glucose or NEFA during the insulin infusion test. The change in 2-hour plasma glucose during the MTT and steady-state plasma glucose during the insulin infusion test also showed no relationship with changes in 2-hour and steady-state plasma NEFA, respectively. These results did not change if sulfonylurea use or BMI were taken into account.

Table 4. 2-Hour and Steady-State Plasma Glucose and NEFA and Serum Insulin During the MTT and Insulin-Dextrose Infusion Test, Respectively (mean ± SD or median and range)

Parameter	Baseline	12 Weeks	Mean Difference (*v* placebo) at 12 Weeks	95% CI
MTT				
2-h glucose (mmol · L^{-1})				
Placebo	14.0 ± 4.2	13.6 ± 3.6		
Acipimox	14.9 ± 3.7	13.5 ± 3.9	−1.4	−2.8, −0.1
2-h insulin (mU · L^{-1})				
Placebo	30 (10-103)	32 (9-86)		
Acipimox	42 (8-87)	33 (12-147)	0.96	0.78, 1.18
2-h NEFA (mmol · L^{-1})				
Placebo	0.23 ± 0.15	0.22 ± 0.12		
Acipimox	0.29 ± 0.16	0.38 ± 0.33	0.19	0.09, 0.29
Insulin infusion test				
SS glucose (mmol · L^{-1})				
Placebo	12.2 ± 4.5	12.8 ± 4.5		
Acipimox	15.2 ± 4.6	14.0 ± 5.9	−1.4	−3.2, 0.5
SS insulin (mU · L^{-1})				
Placebo	55 (36-135)	63 (37-221)	1.08	0.95, 1.24
Acipimox	74 (38-126)	77 (44-138)	(ratio)	
SS NEFA (mmol · L^{-1})				
Placebo	0.10 ± 0.05	0.10 ± 0.06	0.94	0.66, 1.35
Acipimox	0.14 ± 0.07	0.17 ± 0.22	(ratio)	

NOTE. Posttreatment mean differences and 95% CI are shown for difference between acipimox and placebo groups.

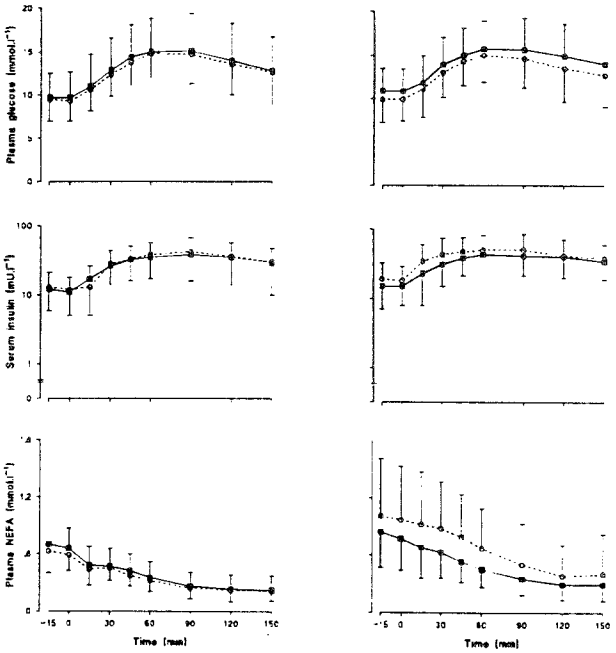

Fig 1. Excursions of plasma glucose, serum insulin, and plasma NEFA during the MTT before (■) and after (○) treatment with placebo (A) or acipimox 500 mg twice daily (B). Results are the mean ± SD.

Table 5. Fasting Serum C-Peptide and Blood 3-Hydroxybutyrate, 2-Hour Plasma Glucose and NEFA During the MTT, and Steady-State Plasma NEFA During the Insulin Infusion Test According to Center

Parameter	Acipimox	Placebo	Mean Difference	95% CI
Fasting C-peptide (ng/mL)				
UK	0.03	0.38	−0.34	−1.69, 1.01
Germany	1.16	−0.31	1.48	0.26, 2.70
Fasting 3-hydroxybutyrate (ratio)				
UK	1.08	1.17	0.91	0.44, 1.87
Germany	2.45	0.98	2.54	0.62, 10.36
MTT				
2-h glucose (mmol · L^{-1})				
UK	1.6	0.3	−1.9	−3.6, −0.2
Germany	−0.6	−0.8	0.2	−1.83, 2.23
2-h NEFA (mmol · L^{-1})				
UK	−0.04	0.01	−0.05	−0.13, 0.03
Germany	0.36	−0.06	0.42	0.17, 0.67
Insulin infusion test				
Steady-state NEFA (ratio)				
UK	0.75	0.86	0.87	0.69, 1.11
Germany	1.66	0.96	1.74	0.97, 3.18

NOTE. Posttreatment mean differences and 95% CI are shown for differences between acipimox and placebo groups. Ratios are shown for the change in steady-state plasma NEFA, as 13 of 33 subjects in the UK and none in Germany were at the detection limit of the assay for plasma NEFA.

Adverse Events and Patient Withdrawals

Eighteen subjects (11 on acipimox and seven on placebo) reported at least one adverse event. Four subjects on the active preparation and two on placebo reported gastrointestinal side effects. Three subjects in each group reported flushing, facial itch, or sweats. There were no significant changes in the full blood cell count or standard biochemical data.

DISCUSSION

We have demonstrated in this study that, compared with placebo, acipimox significantly reduces serum total cholesterol, triglycerides, and apo B. These findings are consistent with previous studies of the drug in both diabetic[19-22] and nondiabetic subjects.[30,31] In vitro experiments on human adipose tissue have shown that acipimox reduces the release of NEFA from adipocytes but has no effect on cholesterol synthesis in jejunal mucosa.[32] The reduced flux of NEFA to the liver reduces the precursor pool for very–low-density lipoprotein synthesis, and so the predominant effect of the drug is on serum triglyceride levels. Although nicotinic acid has been demonstrated to decrease Lp(a) levels,[23,24] acipimox had no effect on Lp(a) in this study. The previous studies with nicotinic acid were not placebo-controlled, and in one study, subjects with Lp(a) less than 30 mg · dL^{-1} were excluded. The findings in this study are more consistent with the results of randomized control trials in which simvastatin and gemfibrozil were shown not to reduce Lp(a) levels.[33-35]

Despite an increase in fasting plasma NEFA with acipimox in this study, we have demonstrated a significant improvement in blood glucose control, as measured by serum fructosamine and glycated hemoglobin, combined with a small nonsignificant decrease in fasting plasma glucose. The observed decrease in fasting plasma glucose (0.5 mmol · L^{-1}) was consistent with the difference the study was designed to detect. It has been demonstrated in a number of short-term studies that other preparations of acipimox result in increasing plasma NEFA with continued use.[14,15] In longer-term studies with standard preparations of acipimox, fasting plasma NEFA levels have not been suppressed.[19,20] However, the sustained-release preparation of acipimox has been shown to reduce plasma NEFA levels over 24 hours in NIDDM subjects,[13] and it was hoped this effect would continue in the long-term. It has been previously shown that similar blood levels of acipimox in the same patient have varying effects on plasma NEFA levels.[14,15] This anomaly may be explained by increased secretion of the counterregulatory hormones, growth hormone and cortisol,[11,12,15] glucagon,[12,15] and epinephrine and norepinephrine,[12] which stimulate lipolysis and therefore increase circulating levels of NEFA and glycerol. The increased rate of lipolysis not only will increase NEFA output by adipocytes but also will hinder reesterification of circulating plasma NEFA, a process already impaired in NIDDM subjects.[36] It is possible that with long-term use, changes in the secretion of these hormones may overcome pharmacological manipulation of lipolytic activity. On the other hand, although fasting plasma NEFA levels did not change from baseline in the treatment group, the decrease in serum triglycerides suggests that NEFA levels will have been lower at several times during the day, hence the real changes in glycemic control.

Although the improvement in glycemic control produced by acipimox (mean reduction of 1.4% in HbA_1) in this study was modest, it compares well with improvements in glycemic control measured by HbA_1 in other recent randomized controlled trials of hypoglycemic agents including acarbose,[37,38] metformin,[39] glibenclamide,[37] tolbutamide,[38] repaglinide,[40] and glimepiride.[41]

Insulin sensitivity as assessed by the insulin-glucose infusion test and response to the MTT apparently did not change during the study. Acipimox had a beneficial effect on insulin sensitivity over 3 months in another study.[19] The subjects were leaner (BMI, 26 kg · m^{-2}) than ours, and this may have contributed to the greater insulin sensitivity. On the basis of no change in fasting plasma NEFA levels, we would not expect an improvement in insulin sensitivity at the time of day this was tested. Acipimox or placebo was taken before the MTT and insulin sensitivity test but after basal samples were collected. On other study days, subjects were instructed to take the study drug on rising. An acute effect of acipimox, decreasing plasma NEFA and improving insulin sensitivity, as previously demonstrated,[9-12] was expected but these changes were not demonstrated. Since fasting plasma NEFA were higher at 12 weeks after acipimox and the hypothesized counterregulatory response giving rise to this unexpected finding may still have been occurring at commencement of the MTT and insulin sensitivity test, the time for acipimox to have an effect on circulating plasma NEFA levels may be prolonged compared with the expected 60 to 90 minutes.[18]

Improvements in glycemic control were demonstrated despite the lack of change in insulin sensitivity or fasting plasma NEFA. No measurement was made of plasma NEFA over 24 hours; however, using the 2 hour plasma NEFA during the MTT as an indicator, there was no relationship with the change in fructosamine or fasting plasma glucose. However, the variation in results between German and UK subjects for some variables suggests that the improvement in glycemic control was due to improved insulin sensitivity (Table 5). Where there was a difference, the changes in UK subjects after acipimox (lower fasting serum C-peptide and blood 3-hydroxybutyrate and lower 2-hour plasma NEFA and glucose in the MTT) were the predicted changes. During the insulin infusion test, steady-state plasma NEFA and glucose were unchanged in both groups; however, the German subjects tended to have a higher steady-state plasma NEFA, consistent with the other findings. Despite the observed differences between the groups, changes in the indices of glycemic control could not be related to changes in fasting plasma NEFA, 2-hour plasma NEFA or glucose in the MTT, or steady-state plasma NEFA or glucose in the insulin infusion test. Changes in HGO were not measured. In NIDDM, strong correlations have been demonstrated between fasting plasma NEFA levels, fasting HGO, and fasting blood glucose[1,42,43] and the rate of NEFA oxidation and rate of HGO.[36] In normal subjects, lipid and heparin infusion (increasing circulating plasma NEFA) increases HGO in the presence of relative insulinopenia.[5,6] If, as suspected, fasting plasma NEFA in the treated subjects were increasing when fasting samples were collected, HGO and therefore fasting glucose may have been affected. This may explain why the fasting glucose did not improve in the treated subjects although the other indicators of

glycemic control, glycated hemoglobin and fructosamine, did improve.

Alternatively, a mechanism of action of acipimox independent of plasma NEFA decreases, could explain the observed improvements in glycemic control in this study. Increased nonoxidative glucose disposal and glycogen synthase activity after acipimox have been demonstrated in NIDDM subjects,[9] as has increased whole-body glucose disposal when plasma NEFA levels are artificially maintained[44]; however, these results are not reproducible when circulating plasma NEFA are reduced before acipimox administration.[45] Nevertheless, since the mechanism of action of acipimox is via the adenylate cyclase/cAMP system,[46,47] further effects of the drug are possible. However, such a mechanism of action may not explain the apparent differences in the response to the drug in this study in different centers.

The possible therapeutic benefits in NIDDM of decreasing circulating plasma NEFA according to the Randle-cycle hypothesis are not clearly evident in this study. Circulating plasma NEFA levels were not adequately suppressed for the full 24-hour period, a problem common to a number of previous studies with the drug. The modest improvement in long-term glycemic control demonstrated in this study suggests that decreasing NEFA may be of benefit in improving glycemic control in NIDDM; however, there appear to be homeostatic mechanisms in place that serve to maintain circulating plasma NEFA levels.

Acipimox in this and previous studies is a useful and well-tolerated lipid-lowering agent in NIDDM and has some beneficial effects on glycemic control and is not associated with the deterioration in blood glucose control seen with nicotinic acid in the past. Since both serum total cholesterol and triglycerides are increased in NIDDM, are predictors of coronary risk in NIDDM patients, and are decreased by acipimox, it should be considered in the management of diabetic dyslipidemia. More potent lipolysis inhibitors may prove more successful in dramatically improving glycemic control.

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