Equivalent Efficacy of a Time-Release Form of Niacin (Niaspan) Given Once-a-Night Versus Plain Niacin in the Management of Hyperlipidemia

R.H. Knopp, P. Alagona, M. Davidson, A.C. Goldberg, S.D. Kafonek, M. Kashyap, D. Sprecher, H.R. Superko, S. Jenkins, and S. Marcovina

This study compared the efficacy and safety of a once-a-night, time-release niacin formulation, Niaspan (Kos Pharmaceuticals, Miami Lakes, FL), with plain niacin and placebo for the treatment of primary hypercholesterolemia. The study was conducted in nine academic lipid research clinics in a randomized, double-blind design. Niaspan 1.5 g at bedtime was compared with plain niacin 1.5 g/d after 8 weeks and 3.0 g/d after 16 weeks in divided doses and with placebo. A total of 223 hypercholesterolemic adult men and women participated. Compared with placebo at 8 weeks, Niaspan versus plain niacin at 1.5 g/d showed comparable efficacy, comparably lowering total cholesterol (C) (8%/8%), triglycerides (16%/18%), low-density lipoprotein (LDL)-C (12%/12%), apolipoprotein (apo B) (12%/12%), apo E (9%/7%), and lipoprotein(a) [Lp(a)] (15%/11%), and raising high-density lipoprotein (HDL)-C (20%/17%), HDL_2-C (37%/33%), HDL_3-C (17%/16%), and apo A-I (8%/6%) ($P \leq .05$ in all instances). After 16 weeks, the Niaspan effect on LDL-C and triglyceride was unchanged while the plain niacin effect approximately doubled. At equal doses of 1.5 g/d of Niapan versus plain niacin, respectively, AST increased 5.0% versus 4.8% (difference not significant [NS]), fasting plasma glucose increased 4.8% versus 4.5% (NS), and uric acid concentrations increased less, 6% versus 16% ($P = .0001$). Flushing events were more frequent with plain niacin versus Niaspan (1,905 v 576, $P < .001$). Flushing severity was slightly greater with Niaspan, but still well tolerated. In conclusion, Niaspan 1.5 g hour of sleep (hs) has comparable efficacy, a lower incidence of flushing, a lesser uric acid rise, and an equivalent hepatic enzyme effect than 500 mg thrice-daily plain niacin in hyperlipidemic subjects. Niaspan may be an equivalent or better alternative to plain niacin at moderate doses in the management of hyperlipidemia.

NIACIN IS A VALUABLE TOOL in the management of hyperlipidemia because of its favorable effect on every aspect of the lipoprotein profile.[1] Niacin raises high-density lipoprotein cholesterol (HDL-C)[2] and reduces low-density lipoprotein cholesterol (LDL-C) and triglyceride levels.[3] Niacin also lowers lipoprotein(a) [Lp(a)].[4] In secondary prevention trials of coronary disease, niacin used alone or in combination with a bile acid–binding resin attained significant reductions in total mortality[5] and coronary disease events,[6] and regression of coronary atherosclerosis.[5,6]

The major limitations to the use of niacin are cutaneous flushing and itching, mucous membrane irritation, including diarrhea, and hepatotoxicity. Although flushing symptoms diminish over time, many patients stop medication prematurely before tolerance develops. An additional limitation to the use of plain niacin is the need to administer the medication two or three times daily.

Time-release niacin preparations have been developed in an attempt to overcome the cutaneous flushing effect of plain niacin, but the available formulations have been less effective and/or more hepatotoxic than plain niacin.[3,7] One of us[7] showed that the sustained-release formulation, Nicobid (Rhone-Poulenc Rorer, Collegeville, PA), is less effective in treating hyperlipidemia than plain niacin at moderate doses and is more toxic above a dose of 1.5 g/d. McKenny et al[3] studied Goldline (Zenith-Goldline, Ft Lauderdale, FL) time-release niacin, where 50% of study patients were withdrawn from therapy before reaching the targeted titration dose of 3 g/d due to elevations in hepatic transaminases. Another time-release formulation, Enduracin (Endurance Products, Tigard, OR), was studied to a dose of only 2 g and was better tolerated,[8] as was Slo-Niacin (Upsher-Smith, Minneapolis, MN) at a mean dose of 1.3 g/d.[9]

The current study tests the efficacy and safety of a new time-release niacin formulation, Niaspan (Kos Pharmaceuticals, Miami, FL), given once daily at bedtime in patients with hyperlipidemia. The rationale for bedtime administration is based on the observation that a nocturnal intravenous infusion of niacin suppresses the night-time rise of plasma free fatty acid levels and the associated increase in plasma triglyceride concentrations.[10-12] A bedtime dose of immediate-release niacin without food would be poorly tolerated and does not suppress the free fatty acid increase throughout the night.[12] Therefore, the time-release niacin formulation, Niaspan, was developed to enable a full day's niacin to be given in a single bedtime dose to minimize flushing symptoms and extend nocturnal efficacy. The present study compares the lipoprotein, hepatic, and metabolic effects of 1.5 g Niaspan hour of sleep (hs) to 1.5 and 3.0 g plain niacin given in three divided doses daily and to placebo.

The maximum Niaspan dose of 1.5 g/d was chosen for study because the metabolism of niacin is saturable at or about this dosage. Pharmacokinetic analyses indicate that single doses of 1.0, 1.5, and 2.0 g of Niaspan per day are associated with peak plasma niacin levels of 0.6, 4.9, and 25.5 μg/mL at 5, 4, and 5 hours postdose, respectively. The duration of drug delivery is 8 to 12 hours. Approximately 60% to 70% of niacin administered as Niaspan in multiple dosages appears in the urine at doses of 1

From the Northwest Lipid Research Clinic, University of Washington, School of Medicine, Seattle, WA; St. Joseph's Heart Institute, Tampa, FL; Chicago Center for Clinical Research, Chicago, IL; Washington University School of Medicine, St Louis, MO; Johns Hopkins University, Baltimore, MD; VA Medical Center, Cholesterol Center, Long Beach, CA; Center for Cholesterol Research, University Hospital, Cincinnati, OH; Berkeley Heart Lab and University of California, Berkeley, CA; and College of Medicine, University of Cincinnati, Cincinnati, OH.

Submitted October 6, 1997; accepted March 4, 1998.

Supported by Kos Pharmaceuticals.

Address reprint requests to R.H. Knopp, MD, Northwest Lipid Research Clinic, #359720, 326 Ninth Ave, Seattle, WA 98104.

0026-0495/98/4709-0012$03.00/0

to 2 g/d. Twelve percent of the dose is recovered in the urine as unchanged niacin.

METHODS

Study Patients

Informed consent was obtained from all participants. Subjects were eligible to participate if after 6 weeks of dietary stabilization on an National Cholesterol Education Program (NCEP) Step One diet, they had an average LDL-C ≥4.9 mmol/L (190 mg/dL), or LDL-C ≥4.1 mmol/L (160 mg/dL) with a clinical history of coronary disease or at least two risk factors for coronary disease. Patients with an HDL-C greater than 1.8 mmol/L (70 mg/dL) were excluded. Patients with uncontrolled or insulin-dependent diabetes mellitus, abnormal liver functions (≥1.3 times upper limit of normal), secondary causes of hyperlipoproteinemia, concomitant medication likely to influence lipid levels, triglyceride concentrations greater than 9.0 mmol/L (800 mg/dL), hypersensitivity to niacin, and/or any major medical problems were excluded. Of 223 subjects qualified for randomization, 13 had baseline triglyceride levels greater than 300 mg/dL, but all values were less than 400 mg/dL. Therefore, the study population is primarily hypercholesterolemic.

Study Design

The design of the 25-week, double-blind, randomized, placebo-controlled study is shown in Fig 1. Subjects underwent a 6-week dietary stabilization period and a 3-week baseline evaluation phase to eliminate patients with greater than 12% variation in LDL-C concentrations. A medical history, physical examination, and ECG were obtained on all patients before randomization. Dietary compliance was monitored using a food-record rating score obtained from 4-day diet diaries. Subjects were randomized equally to three treatment groups: placebo, plain niacin, or Niaspan. All patients were instructed to take four doses of identically appearing tablets daily, once each after meals and at bedtime. The bedtime dose was to be taken with a low-fat snack to minimize the potential for gastrointestinal side effects, although less than half the subjects felt the necessity to comply with this advice. Niaspan was given at bedtime, 375 mg hs in week 1, 500 mg hs in week 2, 750 mg hs in week 3, and 1.5 g hs thereafter and placebo in the three doses taken after meals. The plain niacin group received 125 mg thrice daily in week 1, 250 mg thrice daily in week 2, 500 mg thrice daily in week 3, 1.5 g thrice daily from weeks 4 to 8, and 3.0 g thrice daily from weeks 9 to 16 given as 500 mg tablets with meals and placebo at the bedtime dose. The placebo group received placebo in all four daily doses.

Flushing reactions experienced as redness, warmth, tingling, itching or any combination of these were recorded in a diary. Patients were asked to rate the severity and record the duration of the flushing reaction. Aspirin, generally as 325 mg, was taken as needed one-half hour before taking medication to prevent flushing. Aspirin use, side effects, and adverse events other than flushing were also recorded by the patient in an adverse-event log.

The last three LDL-C values before randomization within 12% of the highest LDL-C determination were averaged to provide the baseline value. During the treatment phase, the average of the LDL-C concentrations at the final three visits was used to measure the effect of the drug in the Niaspan and placebo groups. For the plain niacin group, a single visit (week 8) was used to measure the effect of 1.5 g/d plain niacin and the average of the final two visits (weeks 12 and 16) was used to measure the effect of 3.0 g/d plain niacin. Patients withdrawing from the study before completion were not included in the efficacy analysis, but were included in the safety analysis.

Study Measurements

Fasting blood samples were collected for safety and efficacy determinations at each visit except randomization. Lipid, chemistry, and thyroid profiles were performed at the University Hospital (Cincinnati, OH) Clinical Chemistry Laboratory. The laboratory participates in the Center for Disease Control (CDC) Lipid Standardization Program for lipid analyses and is referenced to the Abel-Kendall method through fresh-sample comparison with the Cholesterol Reference Method Laboratory Network. Total-C was determined by the cholesterol oxidase method and triglycerides by the glycerol blanked enzymatic method (Boehringer Mannheim, Indianapolis, IN). LDL-C was calculated from the Friedewald equation when triglycerides were less than 4.5 mmol/L (400 mg/dL) or by beta quantification when triglycerides were greater than 4.5 mmol/L. Measurement of cholesterol in HDL subfractions, apolipoproteins (apo) A-I, apo B, apo E, and Lp(a) were performed at the University of Washington (Seattle, WA) Northwest Lipid Research Laboratories. Cholesterol in HDL and in HDL_3 subfractions was measured enzymatically on the Abbott Spectrum Analyzer (Abbott Park, IL) on plasma supernatants after precipitation of apo B–containing lipoproteins.[13,14] HDL_2-C was calculated as the difference between HDL and HDL_3 values. Apo A-I and apo B concentrations were measured by a fully automated nephelometer (Boehring Nephelometer Analyzer, Marburg, Germany) calibrated with the International Reference materials for apo A-I and apo B approved by the World Health Organization.[15,16] Lp(a) concentration was determined by an in-house–developed monoclonal antibody–based enzyme-linked immunoadsorbent assay (ELISA) as previously reported.[17] Apo E concentration was measured by an in-house–developed competitive radioimmunoassay performed as previously described.[18] LDL subclass pattern was determined at the Lawrence Berkeley Laboratory (University of California, Berkeley, CA). Plasma was subjected to 2% to 16% polyacrylamide gel electrophoresis. The gels were stained with Oil Red O and the particle size and shape of the major LDL peak determined. Patients were classified as pattern A, AB, or B as follows: (1) pattern A, predominate LDL peak larger than 262 A in diameter with skewing to the right; (2) pattern B, predominate LDL peak less than 255 A with

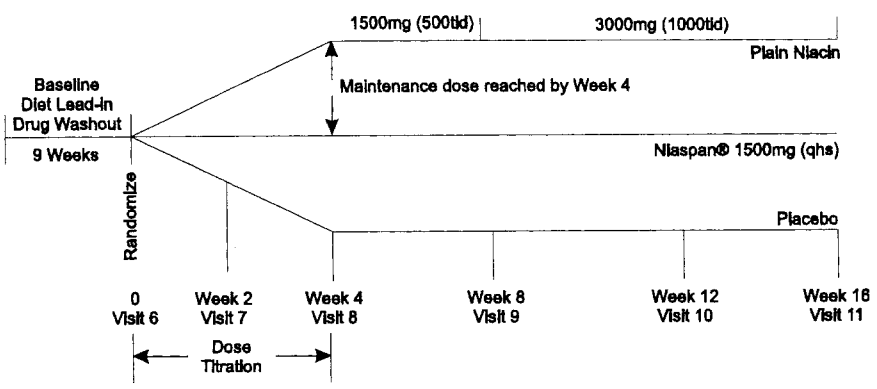

Fig 1. Study schematic showing double-blind treatment for 16 weeks.

skewing to the left; and (3) pattern AB, predominate LDL peak intermediate between 255 and 262 A.

All plasma chemistry measurements were performed using a Hitachi 717 (Boehringer Mannheim, Indianapolis, IN). Thyroid-stimulating hormone and L-thyroxine analyses were performed by chemiluminescence enzyme immunoassay on an ACS-180 (Ciba Corning Diagnostics, Medfield, MA). Complete blood cell count analyses were performed by the Clinical Hematology Laboratory on a Cell Dyne 3500 (Abbott Diagnostics, Abbott Park, IL). Activated partial thromboplastin time and prothrombin analyses were performed on a Medical Laboratory Automation 900c and 1000c (Pleasantville, NY).

Statistical Analyses

The primary measure of efficacy is the change from baseline in LDL-C concentrations of the mean of the 8-, 12-, and 16-week values for Niaspan, the 8-week value for plain niacin 1.5 g, and the mean of the 12- and 16-week values for 3.0 g plain niacin daily versus the mean placebo observations at weeks 8, 12, and 16 (Fig 2). A table of results at 8 and 16 weeks is presented to demonstrate the stability of the values (Table 3). Secondary efficacy outcomes include the change from baseline in total-C, plasma triglyceride, HDL-C, HDL subfractions, apo B, apo A-I, apo E, and Lp(a), and LDL particle size. The primary measures of safety are the change from baseline in hepatocellular enzymes. Other safety measures include the change from baseline in glucose and uric acid concentrations, as well as other chemistry parameters. Drug tolerance was assessed as the number of flushing episodes, reported adverse events, and withdrawal rates.

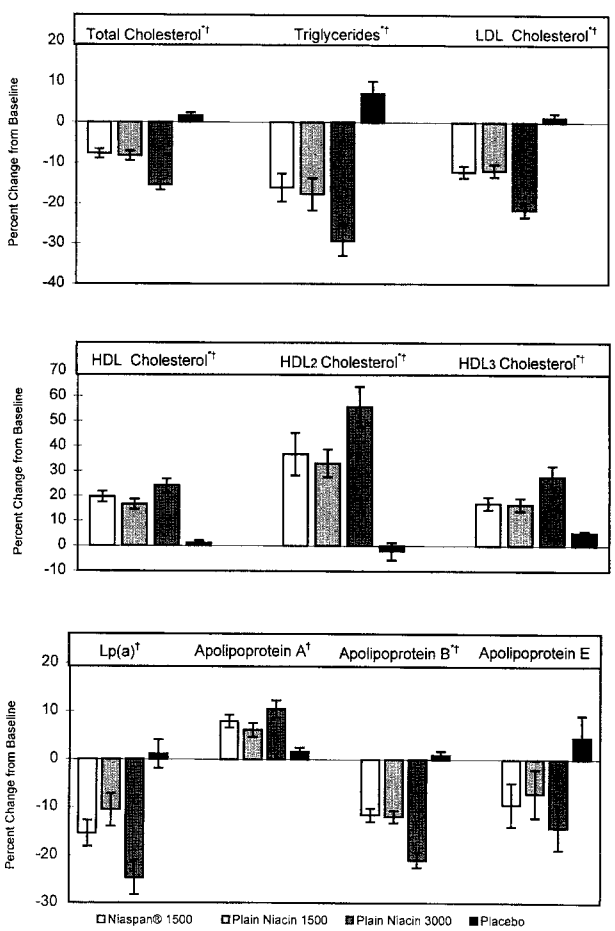

Fig 2. Percent changes from baseline of lipids, lipoproteins, and apolipoproteins. All differences between active treatment and placebo are statistically significant, except for apo E between plain niacin 1,500 mg and placebo ($P = .085$). Niaspan and placebo data are the means of weeks 8, 12, and 16 values. Immediate release niacin data at 1.5 g/d are from week 8 and at 3.0 g/d are the means of weeks 12 and 16 data. *Significant at the .05 level between the Niaspan and plain niacin 3,000 mg. †Significant at the .05 level between plain niacin 1,500 mg and plain niacin 3,000 mg.

Table 1. Characteristics of Study Patients

Parameter	Niaspan (n = 76)	Plain Niacin (n = 74)	Placebo (n = 73)
Demograhics, mean (SE)			
Age (yr)	53 (1.3)	54 (1.3)	55 (1.3)
Gender (male/female)	54/22	52/22	59/14
Body-mass index (kg/m²)	28 (0.5)	28 (0.6)	27 (0.5)
Weight (kg)	84 (1.8)	81 (1.9)	82 (1.7)
Risk factors			
Coronary artery disease	8 (11%)	8 (11%)	7 (10%)
Hypertension	17 (22%)	12 (16%)	11 (15%)
Diabetes	2 (3%)	0 (0%)	0 (0%)
Smoking	3 (4%)	11 (15%)*	7 (10%)
Nutrient intake (% of calories)			
Total fat at baseline	28 (0.7)	30 (0.8)	28 (0.8)
Total fat at end point	29 (0.9)	30 (1.0)	29 (1.0)

*$P < .05$ *v* Niaspan.

Statistical analyses were performed using the SAS (Cary, NC) System for Windows, version 6.10. Baseline values were compared among the study groups to establish that randomization was successful. Baseline values included demographic measurements, initial lipid values, and cardiovascular disease risk factors. The baseline comparisons were conducted using an ANOVA with treatment and study center in the model. This same model was used for outcome analyses of plasma total cholesterol, triglycerides, LDL-C, HDL-C, HDL_2-C, HDL_3-C, apo A-I, apo B, apo E, Lp(a), ALT, AST, alkaline phosphatase, phosphate, uric acid, fasting glucose, 2-hour postprandial glucose, and insulin levels. Within-treatment comparisons were conducted using matched-pair *t* tests between baseline and end point.

Power was determined using an α level of .05 for two-tailed tests, a standard error for the percent change for the LDL-C analyte of 1.65, and a difference between the Niaspan and placebo groups of 13.6%. The power for the approximately 60 patients per group who completed the study was greater than 99%.

RESULTS

Study Subject and Medication Adherence

A total of 739 patients were screened for entry onto the study and 223 qualified for randomization. The baseline characteristics of the patients are shown in Table 1. No significant differences were observed in demographic parameters, nutrient intake, or the prevalence of hypertension, diabetes mellitus, cerebrovascular disease, or coronary heart disease among the treatment groups. Thyroxine (T_4) and thyroid-stimulating hormone (TSH) values were identical among the three groups (data not shown). Fewer smokers were randomized to Niaspan compared with plain niacin (4% *v* 15%, $P = .019$). No significant differences were seen between treatment groups at baseline for plasma lipoprotein lipid, apo B, apo A-I, or Lp(a) levels (Table 2). The mean plasma apo E level (mg/dL) was slightly but statistically significantly lower in the plain niacin group than in the placebo group (Table 2).

Ingestion of study medication measured by pill counts was greater than 90% in all groups. Compliance with the study regimen was similar among treatment groups for all but the first

Table 2. Baseline Plasma Lipoprotein Lipid and Apoprotein Concentration

Analyte	Niaspan	Plain Niacin	Placebo
Lipids and lipoproteins, mean (SE) mmol/L, mg/dL			
Total-C	7.09 (.08)	7.16 (.13)	7.19 (.010)
	274 (3)	277 (5)	278 (4)
Triglyceride	1.86 (.09)	1.73 (.08)	1.70 (.08)
	165 (8)	154 (7)	151 (7)
LDL-C	5.07 (.08)	5.25 (.13)	5.28 (.10)
	196 (3)	203 (5)	204 (4)
HDL-C	1.16 (.03)	1.11 (.03)	1.13 (.03)
	45 (1)	43 (1)	44 (1)
HDL_2-C	.19 (.01)	.18 (.01)	.19 (.01)
	7.2 (.4)	7.0 (.4)	7.3 (.4)
HDL_3-C	.96 (.02)	.91 (.02)	.93 (.02)
	37 (.8)	35 (.9)	36 (.8)
Apolipoproteins, mean (SE) g/L, mg/dL			
Apo E	.058 (.004)	.054 (.004)	.65 (.004)
	5.8 (.4)	5.4 (.4)*	6.5 (.4)
Apo B	1.48 (.02)	1.47 (.03)	1.50 (.02)
	148 (2)	147 (3)	150 (2)
Apo A-I	1.33 (.02)	1.28 (.03)	1.30 (.02)
	133 (2)	128 (3)	130 (2)
Lp(a)	.40 (.05)	.34 (.05)	.31 (.04)
	40 (5)	34 (5)	31 (4)

*$P < .05$ *v* placebo.

visit after randomization, at which compliance with the bedtime Niaspan dose was slightly less than compliance with the daytime plain niacin dose (90% *v* 94%, $P = .041$). No significant changes in body weight were observed between the baseline and final visits in each study group.

Lipoprotein Effects

Data are presented for patients receiving Niaspan at a single dose of 1.5 g/d (mean of weeks 8, 12, and 16), plain niacin at 1.5 g/d after 8 weeks and after titration to 3.0 g/d (mean of weeks 12 and 16), and placebo (mean of weeks 8, 12, and 16) (Fig 2). Results of observations are also presented at 8 or 16 weeks by intent-to-treat (ITT) or efficacy-analyzable (EA) approaches (Table 3). As shown in Fig 2, plasma total-C was significantly reduced by 8%, 8%, and 15%, respectively, by Niaspan, low-dose plain niacin 1.5 g/d, and high-dose plain niacin 3 g/d (Fig 2). For plasma triglycerides, reductions were 16%, 18%, and 29%, respectively, and for LDL-C, 12%, 12%, and 22%, respectively. Reductions in plasma apo B concentrations were 12%, 12%, and 21%, respectively (Fig 2). HDL-C increased by 20%, 17%, and 24%, respectively. HDL_2-C increased 37%, 33%, and 56%, respectively, and HDL_3-C increased 17%, 16%, and 28%, respectively. Apo A-I increased 8%, 6%, and 10%, Lp(a) decreased 15%, 11%, and 25%, and apo E concentrations decreased 9%, 7%, and 14%, respectively. All changes were significantly different from placebo, except the change in apo E level in the plain niacin 1.5-g/d group.

The results in Table 3 confirm these data. Whether subjects are included even if they stopped taking medication (ITT) or were taking medication at 8 or 16 weeks, the results were similar. In addition, there was no consistant change between 8 and 16 weeks in subjects taking 1.5 g Niaspan, while 3 g plain niacin at 16 weeks was clearly better than at 8 weeks. The important point is that the averaged data in Fig 2 are verified by the data obtained at individual time points as shown in Table 3.

Regarding LDL subclass patterns at baseline, 33 of 76 patients in the Niaspan group and 26 of 74 patients in the plain niacin group showed LDL subclass pattern B. After 16 weeks of treatment, 56% of pattern B subjects on Niaspan and 93% of subjects taking 3 g plain niacin daily shifted to pattern A or pattern AB (intermediate pattern) following treatment ($P < .05$), reflecting the higher plain niacin dose.

Safety of Niaspan and Plain Niacin

The mean increase from baseline in hepatic AST was 4.4% ± 2.6% (SE) for Niaspan ($P = .09$) at week 16, and 5.2% ± 3.3% for plain niacin at 1.5 g/d at week 8 ($P = .116$) (Table 4). Two patients in the Niaspan group and one in the plain niacin (1.5 g/d) group had AST concentrations greater than two times the upper limit of normal. No increases of greater than two times

Table 3. Mean Percent Change From Baseline of Various Lipoprotein Parameters

	Placebo				Niaspan 1,500 mg/d				IR Niacin 1,500 mg/d		IR Niacin 3,000 mg/d	
Parameter	ITT-8 (n = 63-78)	EA-8 (n = 47)	ITT-E (n = 62-72)	EA-16 (n = 47)	ITT-8 (n = 63-68)	EA-8 (n = 46)	ITT-E (n = 60-74)	EA-16 (n = 46)	ITT-8 (n = 62)	EA-8 (n = 41)	ITT-E (n = 60-74)	EA-16 (n = 41)
LDL-C	0.9	0.6	0.6	0.2	−10.4*†	−12.1*†	−10.9*†	−13.4*†	−12.3*†	−12.7*†	−19.8*†	−20.9*†
Apo B	0.9	0.9	1.3	0.8	−10.9*†	−11.4*†	−12.2*†	−12.5*†	−11.9*†	−12.0*†	−21.0*†	−20.7*†
HDL-C	0.4	0.5	1.7	2.2	18.2*†	18.5*†	17.1*†	19.0*†	18.7*†	16.8*†	25.7*†	24.4*†
Apo A-1	1.2	0.8	2.0	1.1	8.3*†	7.9*†	7.5*†	7.1*†	7.1*†	7.6*†	10.5*†	11.0*†
Total-C	1.2	1.0	1.6	1.8	−6.4*†	−7.7*†	−6.6*†	−8.0*†	−8.3*†	−8.2*†	−13.6*†	−14.0*†
Triglyceride	6.3	5.8	10.5*	13.9*	−14.3*†	−14.9*†	−10.7*†	−9.8*†	−17.3*†	−12.9*†	−26.5*†	−23.9*†
VLDL	6.7	6.2	10.2*	13.8*	−14.5*†	−15.1*†	−10.2*†	−9.5†	−17.4*†	−13.4*†	−26.5*†	−23.9*†
HDL_2	−1.8	−0.9	−2.6	−2.7	36.7*†	37.1*†	35.4*†	31.7*†	35.6*†	32.0*†	55.8*†	53.5*†
HDL_3	4.1*	2.9	4.8*	4.0*	16.0*†	16.8*†	16.4*†	16.8*†	18.4*†	16.3*†	27.5*†	25.9*†
Apo E	0.3	0.8	8.6	11.9	−10.9*	−15.3*†	−7.8†	−8.6†	−7.2	−5.1	−14.3*†	−13.5*†
Lp(a)	0.4	−2.0	2.2	−2.2	−17.3*†	−19.4*†‡	−14.9*†	−20.2*†	−10.1*†	−7.4	−24.7*†	−25.9*†

Abbreviations: IR, immediate release; ITT, intent to treat; EA, efficacy analyzable; 8, 8 weeks; 16, 16 weeks; E, end point, ie, last study visit.

*Significantly different ($P < .05$) from baseline by matched-pair *t* test comparing baseline and visit levels.

†Significantly different ($P < .05$) from placebo by ANOVA with site and treatment in model.

‡Significantly different ($P < .05$) for Niaspan *v* IR niacin.

Table 4. Effect of Niacin Treatment on Serum AST and ALT by Week

	Baseline	Week 2	Week 4	Week 8†	Week 12‡	Week 16‡
AST						
Niaspan						
Observed value (IU/L)	21.8	21.3	22.8	23.8	21.9	22.1
% change from baseline	NA	−0.9	4.5	10.7*	4.0	4.4
Plain niacin						
Observed value (IU/L)	21.8	21.1	22.8	22.2	24.1	23.4
% change from baseline	NA	−1.4	7.2*	5.2	14.7*	10.8*
ALT						
Niaspan						
Observed value (IU/L)	21.8	21.6	21.1	20.7	20.0	20.3
% change from baseline	NA	−0.5	−1.5	−0.2	−3.7	−2.4
Plain niacin						
Observed value (IU/L)	21.0	19.4	20.0	19.1	20.4	19.9
% change from baseline	NA	−4.2	0.7	−3.8	7.6	3.1

Abbreviation: NA, not applicable.
*$P < .05$ *v* baseline.

the upper limit of normal were observed for ALT concentrations in either Niaspan or plain niacin groups. A significant mean AST increase above baseline of 10.7% was observed at the 8-week visit in the Niaspan group, but this increase was not sustained in later visits (Table 3), while plain niacin at 3.0 g/d was associated with rises of 14.7% and 10.8% at weeks 12 and 16. No significant increases in ALT were observed on any regimen.

Fasting plasma glucose concentrations increased slightly but significantly at doses of 1.5 g/d in both the Niaspan and plain niacin groups ($P < .001$) (mean ± SE): 5.3% ± 1.1% and 4.4% ± 1.2%, respectively. At 3.0 g/d of plain niacin, mean fasting glucose concentrations ± SE increased by 7.3% ± 1.8%. A total of four patients (5.3%) in the Niaspan group and three (4.1%) in the plain niacin group had an increase in fasting blood glucose above 7.77 mmol/L (140 mg/dL) following treatment. No subjects displayed such a glucose increase in the placebo group.

The mean ± SE percentage increase in uric acid concentrations was 5.8% ± 1.7% for Niaspan and 16.2% ± 1.4% for the plain niacin (1.5 g/d) group ($P \leq .001$). At 3.0 g/d plain niacin, mean uric acid levels ± SE increased 22.6% ± 2.5% from baseline. One subject in the Niaspan group developed gout after doubling the prescribed dose of drug for 4 days at his own initiative. No significant change in plasma uric acid level was seen in the placebo group.

A significant decrease in serum phosphorus concentrations was observed with both the Niaspan and plain niacin formulations. The mean ± SE decrease from baseline was 6.9% ± 1.7% and 5.7% ± 1.5% in the Niaspan and plain niacin (1.5 g/d) groups, respectively ($P < .001$ in both instances). At 3.0 g/d of plain niacin, the phosphorus level was slightly more decreased, to 7.6% ± 1.6% from baseline. To our knowledge, decreases in phosphorus concentrations have not been reported previously with niacin therapy. More than 20 other blood and urinary physiological parameters were monitored throughout the study, including other liver function tests, and no statistically or clinically significant differences were observed in any treatment group.

Tolerance to the Niacin Formulations

During the titration phase of the study (weeks 1 and 2), significantly more patients flushed with plain niacin compared with Niaspan (54 *v* 26, $P < .001$; Fig 3). Thereafter, the number of patients reporting flushing events on each regimen did not differ. The number of patients who flushed on either niacin preparation decreased over the duration of the study, and by the final visit, 33% of Niaspan patients and 44% of plain niacin patients continued to report flushing episodes. As expected, the total number of flushing events was significantly higher in the plain niacin group given three times a day compared with the Niaspan group given once a night, comprising a total of 1,905 versus 576 episodes at all visits, $P < .001$ (Fig 4). In the Niaspan group, the flushing reaction occurred, on average, 3 hours after ingesting medication, compared with an average of 90 minutes in the plain niacin group. A few patients in the Niaspan group were awakened at night with flushing, but this symptom was not sufficient to discontinue medication. The intensity of the flushing episodes experienced by Niaspan users tended to be greater than those taking plain niacin, but was not associated with a greater dropout rate (see later). For instance, on a scale of 1 to 100, severity at 8 weeks was 46.4% with Niaspan, 35.3% with plain niacin, and 38.3% with placebo. Respective estimates at week 16 were 48.1%, 30.5%, and 37.7%.

No significant differences in gastrointestinal complaints, pruritus, or rash were observed between the three treatments. Adverse gastrointestinal reactions were reported by 42% of patients in the Niaspan group, 39% in the plain niacin group, and 43% in the placebo group. Pruritus was reported by 3% of Niaspan patients, 7% of plain niacin patients, and 2% of placebo controls. Rash was reported by 6% of Niaspan patients, 10% of plain niacin patients, and 2% of placebo controls. No pruritus or rash events were reported by Niaspan patients during the final 8 weeks of the study.

Subject Withdrawal

Eight subjects in the Niaspan group and 12 in the plain niacin group withdrew due to adverse effects attributable to study drug

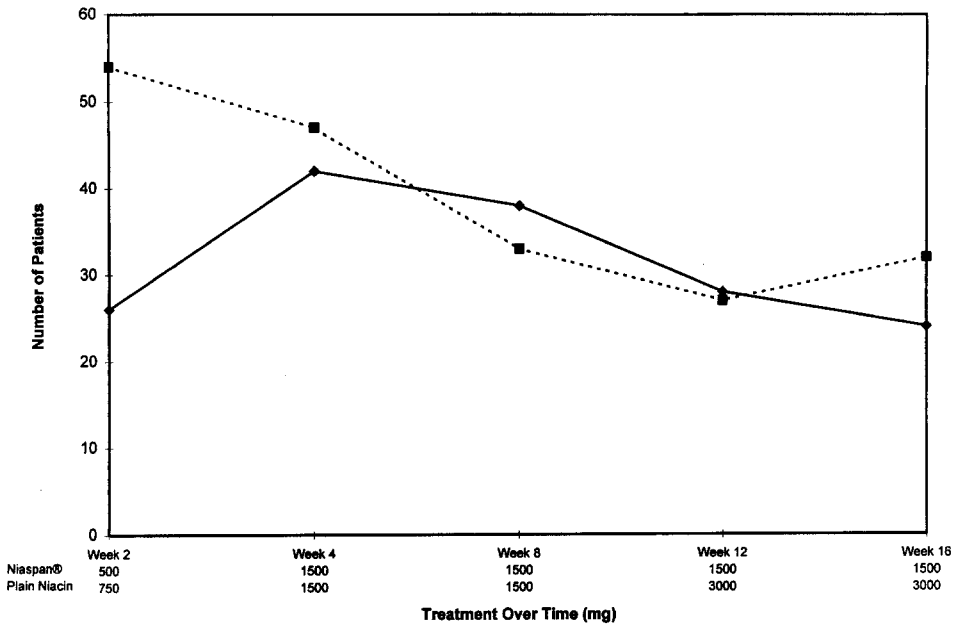

Fig 3. Number of study patients flushing at each visit following randomization to niacin. Data are shown for Niaspan (–◆–) and plain niacin (. . . ■ . . .) patients.

treatment. Subjects withdrew in the Niaspan group due to gout (n = 1), gastrointestinal (GI) distress (n = 2), oral ulcerations (n = 1), flushing (n = 3), and increased (>2 times the upper limit of normal) liver enzymes (n = 1), for a total of eight. Withdrawals due to adverse events in the plain niacin group included GI distress (n = 4), rash (n = 2), pruritus (n = 1), increased (>3 times the upper limit of normal) liver enzymes (n = 1), flushing (n = 3), and elevated uric acid level (n = 1), for a total of 12.

DISCUSSION

A key mechanism in the pathogenesis of hyperlipidemia is the rate of fatty acid mobilization from adipose tissue, which in turn influences the rate of hepatic triglyceride secretion in the form of very–low-density lipoprotein (VLDL)-C.[19,20] Because VLDL-C is subsequently converted in part to LDL-C, overproduction of VLDL-C can lead to an excess of VLDL-C, LDL-C, or both depending on the ability of the body to remove these two lipoprotein species. These interrelating mechanisms account for the several different hyperlipidemic phenotypes of combined hyperlipidemia appearing within a family or an individual at different times.[21]

Interruption of the delivery of free fatty acids to the liver, especially at night, has the ability to lower plasma triglyceride levels by reducing hepatic overproduction. Shlierf and Dorow were the first to show this effect with intravenous infusions of both glucose and niacin.[10,11] Later, they observed a lesser triglyceride reduction with sustained-release niacin formula-

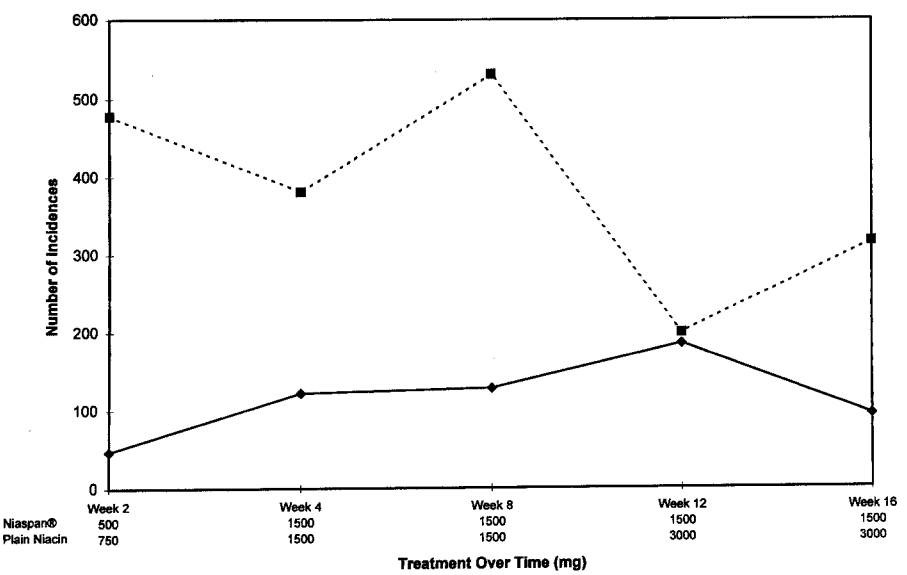

Fig 4. Total number of flushing incidences per visit. Data are shown for Niaspan and (–◆–) and plain niacin (. . . ■ . . .) patients.

tions given at bedtime.[12] However, no attempt appears to have been made to measure the effect of hs niacin administration on plasma LDL-C levels.

The present study represents the first attempt to reduce LDL-C levels by administering a once-a-night, time-release form of niacin, designed to exert the majority of its effect during the nocturnal hours. This research compares a bedtime dose of Niaspan to plain niacin given in three doses daily with meals.

The results show that 1.5 g/d of Niaspan or plain niacin given for 8 weeks yield equivalent benefits on all lipoprotein parameters studied. These results represent the first demonstration to our knowledge of a single dose of niacin being equivalent to a divided dose of niacin regardless of the form. The clinical advantage of this observation is that an equivalent but better tolerated and more convenient alternative exists to plain niacin at a dose of 1.5 g/d for the management of combined hyperlipidemia.

Direct comparisons of other time-release niacin formulations with plain niacin are few. When Nicobid was compared with plain niacin, plasma triglyceride reductions and HDL-C increases were significantly less.[7] In addition, Nicobid was poorly tolerated above 2 g/d, explaining in part the poorer effect on all lipoprotein fractions above this level. A similar result was seen with Enduracin[8] at doses of 2 g/d versus baseline, where triglycerides decreased 11% and HDL-C increased only 4%. In the study of Goldline sustained-release niacin, triglyceride reductions and HDL-C increases were less than those seen with plain niacin,[3] while a notable increase in hepatotoxicity was observed at doses $\geq$2 g/d.

The effect of niacin on LDL subclass characteristics (patterns A and B) is of interest, since an elevation in the number of small, dense LDL particles is associated with premature coronary artery disease[20] and with combined hyperlipidemia.[20-26] Previously, Superko[27] showed a shift in LDL particle size from pattern B (small, dense LDL) to pattern A (large, buoyant LDL) in 59% of pattern B patients following treatment with plain niacin (mean dose, 1,875 mg/d). In the present study, Niaspan resulted in a shift from pattern B to pattern A or pattern AB in 56% of pattern B patients. Plain niacin was even more effective, resulting in a shift to pattern A or AB in 93% of pattern B patients at a dose of 3 g/d. Thus, LDL subclass pattern B can be shifted toward pattern A by both forms of niacin.

The combined hyperlipidemias are the most common of the hyperlipidemic conditions, are the most vexing to treat, and are the lipid disorders most commonly associated with coronary artery disease presenting in physicians' offices. A dose of 1.5 g of Niaspan daily is effective in obtaining triglyceride, LDL-C, and HDL-C benefit, confirming a previous study of Niaspan alone. If needed, further LDL-C lowering can be obtained by adding a low-dose reductase inhibitor. An evaluation of the safety and efficacy of Niaspan with reductase inhibitors is planned. Two recent trials of plain niacin with reductase-inhibitor therapy of hypercholesterolemia have demonstrated the efficacy of this drug combination.[29,30]

Hepatotoxicity is a major cause of morbidity with time-release niacin formulations,[31] is dose-related, and most often occurs at daily doses greater than 2 g/day.[3,7] Several cases of fulminant hepatic failure have been reported in patients taking high-dose (>2 g/d) time-release niacin.[32,33] However, no clinically significant hepatic dysfunction was observed in patients receiving 1.5 g/d Niaspan. Regarding other time-release formulations, asymptomatic elevations of AST in 2.6% of individuals taking Enduracin,[8] significantly higher alkaline phosphatase levels, and a trend toward higher AST concentrations in patients taking Nicobid than those taking plain niacin[7] and AST levels increased 154% with Goldline SR niacin at a dose of 1.5 g/d.[3] At a dose of 1.5 g/d of Niaspan, AST elevations were increased approximately 5% above baseline and were indistinguishable from plain niacin.

Niaspan increased fasting blood glucose concentrations by 4.8%. This increase compares with a reported 3.6% increase in fasting blood glucose with Enduracin,[8] a 22% increase with Nicobid,[7] and a 9.3% increase with Goldline SR niacin.[3] Direct comparisons of the various time-release agents on glycemic status are needed, as are studies of the possible utility and safety of Niaspan in diabetic patients. Regarding 2-hour postprandial glucose, baseline values (mean $\pm$ SE) were 111 $\pm$ 5, 102 $\pm$ 5, and 116 $\pm$ 6 mg/dL with Niaspan, plain niacin, and placebo, respectively. At the end of the study, corresponding postprandial glucose values were 122 $\pm$ 6, 116 $\pm$ 6, and 118 $\pm$ 7 mg/dL. Corresponding immunoreactive insulin (IRI) levels at baseline were 64 $\pm$ 6, 62 $\pm$ 8, and 67 $\pm$ 10 pmol/L. At the end of the study, IRI levels were 77 $\pm$ 8, 71 $\pm$ 9, and 67 $\pm$ 9 pmol/L, respectively. None of the postprandial glucose or insulin values were different at the end of the study among the three groups of subjects.

Niacin is known to increase uric acid concentrations and may precipitate gout, but the uric acid elevation was significantly less elevated with Niaspan compared with plain niacin. A similar finding was reported with Nicobid compared with plain niacin,[7] where uric acid increased 89 μmol/L (1.5 mg/dL) with plain niacin, but only 5.95 μmol/L (0.1 mg/dL) with Nicobid.

Cutaneous flushing reactions occur in 80% to 90% of plain niacin users and may adversely affect medication compliance. During the niacin escalation phase of the study, fewer patients randomized to Niaspan reported flushing compared with plain niacin patients, and the incidence of flushing events throughout the study was significantly less with Niaspan than with plain niacin. Flushing in the middle of the night occurred occasionally in Niaspan users and was relieved by taking an aspirin tablet or taking the medication a few hours before bedtime, but, in general, Niaspan was surprisingly well tolerated. In other time-release formulations, flushing was reported in 1.2% of patients receiving Enduracin,[8] 82% of patients taking Nicobid,[7] and none in patients taking Goldline SR niacin.[3]

In summary, a new time-release niacin formulation, Niaspan, given at bedtime has comparable or slightly better lipid-altering efficacy and safety comparable to plain niacin at a dose of 1.5 g/d. Niaspan administered at bedtime appears to be an effective alternative to plain niacin in the hypercholesterolemia and combined hyperlipidemia.

ACKNOWLEDGMENT

The authors wish to acknowledge Phillip Simmons for assistance with statistical analyses.

REFERENCES

1. National Cholesterol Education Program Expert Panel: Summary of the second report of the National Cholesterol Education Program expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel II). JAMA 269:3015-3023, 1993
2. Luria MH: Effect of low-dose niacin on high-density lipoprotein cholesterol and total cholesterol/high-density lipoprotein cholesterol ratio. Arch Intern Med 148:2493-2495, 1988
3. McKenney JM, Proctor JD, Harris S, et al: A comparison of the efficacy and toxic effects of sustained- vs immediate-release niacin in hypercholesterolemic patients. JAMA 271:672-677, 1994
4. Carlson LA, Hamsten A, Asplund A: Pronounced lowering of serum levels of lipoprotein Lp(a) in hyperlipidemic subjects treated with nicotinic acid. J Intern Med 226:271-276, 1989
5. Canner PL, Berge KG, Wenger NK, et al: Fifteen year mortality on Coronary Drug Project patients: Long-term treatment with niacin. J Am Coll Cardiol 8:1245-1255, 1986
6. Blankenhorn DH, Nessim SA, Johnson RL: Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary bypass grafts. JAMA 257:3233-3240, 1987
7. Knopp R, Ginsberg J, Albers JJ: Contrasting effects of unmodified and time-release forms of niacin on lipoproteins in hyperlipidemic subjects: clues to mechanism of action of niacin. Metabolism 34:642-650, 1985
8. Keenan JM, Fontaine PL, Wenz JB, et al: Niacin revisited: A randomized, controlled trial of wax-matrix sustained-release niacin in hypercholesterolemia. Arch Intern Med 151:1424-1432, 1991
9. Squires RW, Allison TG, Gau GT, et al: Low-dose, time-release nicotinic acid: Effects in selected patients with low concentrations of high density lipoprotein cholesterol. Mayo Clin Proc 67:855-860, 1992
10. Schlierf G, Dorow E: Diurnal patterns of triglycerides, free fatty acids, blood sugar, and insulin during carbohydrate-induction in man and their modification by nocturnal suppression of lipolysis. J Clin Invest 52:732-740, 1973
11. Schlierf G, Hess G: Inhibition of carbohydrate-induced hypertriglyceridemia by nicotinic acid. Artery 3:174-179, 1977
12. Kruse W, Kruse W, Raetzer H, et al: Nocturnal inhibition of lipolysis in man by nicotinic acid and derivatives. Clin Pharmacol 16:11-15, 1979
13. Warnick GR, Benderson J, Albers JJ: Dextran sulfate-Mg^{2+} precipitation procedure for quantitation of high density lipoprotein cholesterol. Clin Chem 28:1279-1288, 1982
14. Bachorik PS, Albers JJ: Precipitation methods for quantitation of lipids, in Albers JJ, Segrest JP (eds): Methods in Enzymology. Orlando, FL, Academic, 1986, pp 78-100
15. Marcovina SM, Albers JJ, Henderson LO, et al: International Federation of Clinical Chemistry standardization project for measurements of apolipoproteins A-I and B. III. Comparability of apo A-I values by the use of international reference material. Clin Chem 39:773-781, 1993
16. Marcovina SM, Albers JJ, Kennedy H, et al: International Federation of Clinical Chemistry standardization project for measurements of apolipoproteins A-I and B. IV. Comparability of apo B by the use of international reference material. Clin Chem 40:586-592, 1994
17. Marcovina SM, Albers JJ, Gabel B, et al: The effect of the number of apo(a) kringle 4 domains on the immunochemical measurement of Lp(a). Clin Chem 41:246-255, 1995
18. Applebaum-Bowden D, McLean P, Steinmetz A, et al: Lipoprotein, apolipoprotein, and lipolytic enzyme changes following estrogen administration in postmenopausal women. J Lipid Res 30:1895-1906, 1989
19. Sniderman AD, Cianflone K: Substrate delivery as a determinant of hepatic apoB secretion. Arterioscler Thromb 13:629-636, 1993
20. Kwiterovich PO, Motevalli M, Miller M, et al: Further insights into the pathophysiology of hyperapobetalipoproteinemia. Clin Chem 37:317-326, 1991
21. Venkatesan S, Cullen P, Pacy P, et al: Stable isotopes show a direct relation between VLDL apoB overproduction and serum triglyceride levels and indicate a metabolically and biochemically coherent basis for familial combined hyperlipidemia. Arterioscler Thromb 13: 1110-1118, 1993
22. Austin MA, King MC, Vranizan KM, et al: Atherogenic lipoprotein phenotype. A proposed genetic marker for coronary heart disease risk. Circulation 82:495-506, 1990
23. Brunzell JD, Albers JJ, Chait A, et al: Plasma lipoproteins in familial combined hyperlipidemia and monogenic familial hypertriglyceridemia. J Lipid Res 24:147-155, 1983
24. Kwiterovich PO, White S, Forte T, et al: Hyperapobetalipoproteinemia in a kindred with familial combined hyperlipidemia and familial hypercholesterolemia. Arterioscler Thromb 7:211-225, 1987
25. Williams RR, Hunt SC, Hopkins PN, et al: Familial dyslipidemia hypertension: Evidence from 58 Utah families for a syndrome present in approximately 15% of patients with essential hypertension. JAMA 259:3579-3586, 1988
26. Reaven GM: Banting Lecture 1988: Role of insulin resistance in human disease. Diabetes 37:1595-1607, 1988
27. Superko HR, Krauss RM: Differential effects of nicotinic acid in subjects with different LDL subclass patterns. Atherosclerosis 95:69-76, 1992
28. Morgan JM, Capuzzi DM, Guyton JR, et al: Treatment effect of Niaspan, a controlled-release niacin, in patients with hypercholesterolemia: A placebo-controlled trial. J Cardiovasc Pharmacol Therapeut 1:195-202, 1996
29. Davignon J, Roederer G, Montigny M, et al: Comparative efficacy and safety of pravastatin, nicotinic acid and the two combined in patients with hypercholesterolemia. Am J Cardiol 73:339-345, 1994
30. Stein EA, Davidson MH, Dujovne CA, et al: The efficacy and tolerability of low dose simvastatin and niacin, alone and in combination, in patients with combined hyperlipidemia: A prospective trial. J Cardiovasc Pharmacol Therapeut 1:107-116, 1996
31. Knopp RH: Niacin and hepatic failure. Ann Intern Med 111:769, 1989
32. Clementz GL, Holmes AW: Nicotinic acid-induced fulminant hepatic failure. J Clin Gastroenterol 9:582-584, 1987
33. Mullin G, Greeson JK, Mitchel MC: Fulminant hepatic failure after ingestion of sustained-release nicotinic acid. Ann Intern Med 111:253-255, 1989