Multiple-Dose Efficacy and Safety of an Extended-Release Form of *Niacin* in the Management of Hyperlipidemia

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This multicenter trial evaluated the safety and efficacy of escalating doses of Niaspan (niacin extended-release tablets) and placebo (administered once-a-day at bedtime) in patients with primary hyperlipidemia on the percent change from baseline in levels of low-density lipoprotein (LDL) cholesterol and apolipoprotein B. Extended-release niacin was initiated at a dose of 375 mg/day, raised to 500 mg/day, and further increased in 500-mg increments at 4-week intervals to a maximum of 3,000 mg/day. A total of 131 patients (n = 87, extended-release niacin; n = 44, placebo) were treated for 25 weeks with study medication after a 6-week diet lead-in/drug washout phase and 2-week baseline LDL cholesterol stability phase. Significant decreases from baseline in levels of LDL cholesterol and apolipoprotein B became apparent with the 500-mg/day dose and were consistent at all subsequent doses ($p \leq 0.05$), reaching 21% and 20%, respectively, at the 3,000-mg/day dose. Significant increases from baseline in levels of high-density lipoprotein cholesterol became apparent with the 500-mg/day dose and were consistent at all subsequent doses ($p \leq 0.05$), reaching 30% at the 3,000-mg dose. Significant decreases from baseline in triglycerides and lipoprotein(a) occurred at the 1,000-mg dose and were apparent at all subsequent doses ($p \leq 0.05$), reaching 44% and 26%, respectively, at the 3,000-mg dose. The most common adverse events were flushing and gastrointestinal disturbance. Transaminase increases were relatively small, and the proportion of patients who developed liver function abnormalities on extended-release niacin was not significantly different from placebo. Thus, extended-release niacin was generally well tolerated and demonstrated a dose-related ability to alter favorably most elements of the lipid profile.

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Niacin (nicotinic acid) exerts its lipid-lowering effect by inhibiting the production of very-low-density lipoprotein (VLDL) particles by the liver, and consequently reducing the level of circulating VLDL available for conversion to low-density lipoprotein (LDL).[1] Niacin has also been demonstrated to lower levels of LDL cholesterol by 10% to 25%,[1] triglyceride levels by 20% to 50%,[1,2] and raise levels of high-density lipoprotein (HDL) cholesterol by 15% to 35%.[1,3] The triglyceride-lowering and HDL cholesterol-raising effects of niacin may be more pronounced in patients with a predominance of small, dense LDL, which has been associated with increased risk for coronary heart disease.[4] Moreover, in these patients, niacin therapy also appears to normalize the proportion of small, dense LDL to more buoyant LDL particles.[4] Data from the Framingham Study indicate that a substantial portion of coronary heart disease events occur in patients with moderate or low levels of total cholesterol or LDL cholesterol, but who have significant mixed dyslipidemia, such as low levels of HDL cholesterol, elevated lipoprotein(a), or elevated triglycerides.[5] Because niacin positively effects multiple lipid parameters, it is an ideal agent for patients with mixed dyslipidemia. However, the incidence of adverse effects associated with immediate-release niacin, including flushing, itching, gastrointestinal upset, and hepatotoxicity, have limited physician and patient acceptance.[6] In addition, the need for multiple dosing of immediate-release formulations hinders patient compliance. Sustained-release niacin preparations are associated with reduced rates of flushing, but can produce increases in serum levels of hepatic transaminases and, rarely, hepatic failure.[2,7–10] Niaspan (Kos Pharmaceuticals, Inc., Miami, Florida) is an extended-release form of niacin with intermediate-release characteristics that is also dosed once each night when cholesterol synthesis and fatty acid mobilization are at their peak, and is thus designed to minimize both liver enzyme elevations and flushing. The current trial was conducted to compare the safety and efficacy of increasing daily doses of extended-release niacin, from 500 to 3,000 mg/day, with placebo when dosed once each night at bedtime in combination with an appro-

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TABLE I Baseline Demographics

	Extended-Release Niacin (n = 87)	Placebo (n = 44)
Age (yrs)	54	55
Men (no. %)	50 (57%)	27 (61%)
Caucasian (no. %)	78 (90%)	41 (93%)
Height (cm)	170	170
Weight (kg)	81	82
LDL cholesterol (mg/dl)	224	208
HDL cholesterol (mg/dl)	46	44
Triglycerides (mg/dl)	183	198
Apolipoprotein B (mg/dl)	167	160

p = NS for all demographics in extended-release niacin versus placebo groups.

priate diet in patients with primary hyperlipoproteinemia.

METHODS

Patient population: Men and women 21 to 75 years of age were recruited at 8 sites. Table I shows baseline characteristics of the 131 subjects. The study was approved by institutional review boards at all sites and all patients signed an informed consent document.

Patients were required to meet criteria for average baseline LDL cholesterol and risk factors for coronary heart disease based on guidelines of the National Cholesterol Education Program[11]: an average baseline LDL cholesterol level of ≥190 mg/dl and no coronary heart disease risk factors, or an average value >160 and <190 mg/dl with a minimum of 2 coronary heart disease risk factors. Criteria for exclusion included secondary hyperlipoproteinemia, type I or uncontrolled type II diabetes mellitus, baseline alanine aminotransferase levels >1.3 times the upper limit of normal, active peptic ulcer disease, gout, and hyperuricemia.

Study design: This multicenter, double-blind, diet- and placebo-controlled trial began with a 6-week, diet run-in/drug washout period followed by a 2-week phase to determine LDL cholesterol stability. The total duration of study medication treatment was 25 weeks. The first treatment visit was 5 weeks after randomization, and remaining visits were 4 weeks apart. Fasting blood samples (12-hour minimum) were collected at each treatment visit for lipid analysis and safety monitoring. Chemistry laboratory tests were performed at all visits, and hematologic testing was performed periodically. Dietary compliance to National Cholesterol Education Program step l diet was monitored by reviews of patient-recorded logs at each visit by appropriately trained counselors.

Patients were randomized to placebo (n = 44) or extended-release niacin (n = 87) at week 1 and were instructed to take 1 dose at bedtime. Initial dosing with extended-release niacin was 375 mg/day during week 1 and was increased to 500 mg/day at week 2. Dosing was then increased by 500 mg/day at 4-week intervals to a maximum of 3,000 mg/day.

Patients were instructed to record all flushing reactions, defined as redness, warmth, tingling, itching, or any combination of these. Patients were permitted to take one 325 mg aspirin 30 minutes before study medication dosing as needed to prevent flushing.

Study measurements and statistical analyses: The primary measure of efficacy was the change from baseline in LDL cholesterol and apolipoprotein B levels. Secondary measures of efficacy were change from baseline in total cholesterol, HDL cholesterol, VLDL, plasma triglycerides, HDL subfractions, apolipoprotein A-1, and lipoprotein(a).

For lipoprotein analyses, blood was collected after a 12- to 14-hour overnight fast and transferred at 4°C by overnight express to a central laboratory (Lipid Research Core Laboratory, Washington University School of Medicine, St. Louis, Missouri). Total cholesterol and triglycerides were analyzed by enzymatic methods (Technicon, Tarrytown, New York). HDL cholesterol was isolated using dextran sulfate/magnesium precipitation,[12] and LDL cholesterol was calculated by the Friedewald equation. In patients with triglycerides >400 mg/dl, LDL cholesterol was determined by ultracentrifugation.[13] The laboratory maintained National Heart, Lung, and Blood Institute Part III Standardization for lipid parameters. Apolipoprotein A-1, apolipoprotein B, and lipoprotein(a) were measured at the Northwest Lipid Research Laboratory, Seattle, Washington. Apolipoprotein A-1 and apolipoprotein B were measured by nephelometry and lipoprotein(a) by competitive enzyme-linked immunosorbent assay. Safety laboratory, chemistry, and hematologic results were measured using standard methods.

The baseline comparisons were conducted using an analysis of variance for each population across all visits. Within-group analyses to assess the significance of mean percent changes from baseline at each treatment visit were calculated with matched-pair *t* tests. A multiple comparison F test was performed to assess the dose-response of extended-release niacin. Statistical comparisons of adverse events were conducted using Fisher's exact and chi-square tests. Sample size was selected to ensure the ability to detect a difference of at least 8% in LDL cholesterol levels between extended-release niacin and placebo.

RESULTS

A total of 132 patients were randomized; 1 patient did not receive study medication. Of those randomized, 80 patients completed the study and 51 terminated the study early. Of those who terminated the study, 31 patients withdraw because of medical reasons (30% and 11% in the extended-release niacin and placebo groups, respectively) and 20 were withdrawn for nonmedical reasons such as relocation, protocol violation, or being lost to follow-up. Of the 26 patients discontinued from the extended-release niacin group, 8 withdrew because of flushing (all before the 2,000-mg/day dose) and 5 because of rash. These reasons accounted for half of the "drop outs" in the extended-release niacin group. The remaining patients were withdrawn owing to several reasons including weak-

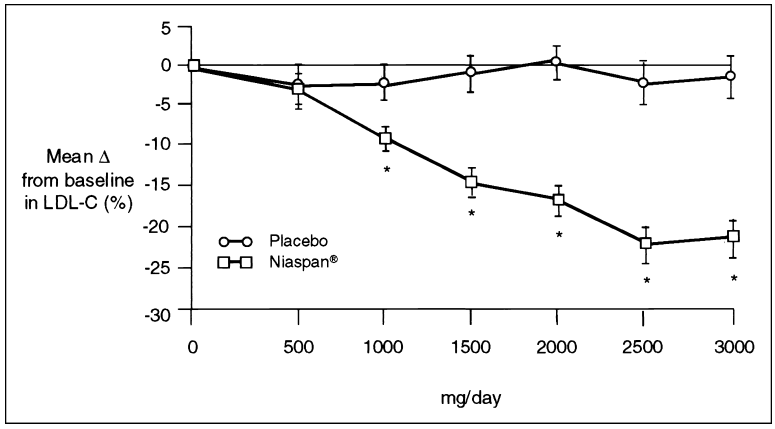

FIGURE 1. Mean percent change from baseline in LDL cholesterol. *p ≤0.05 versus placebo.

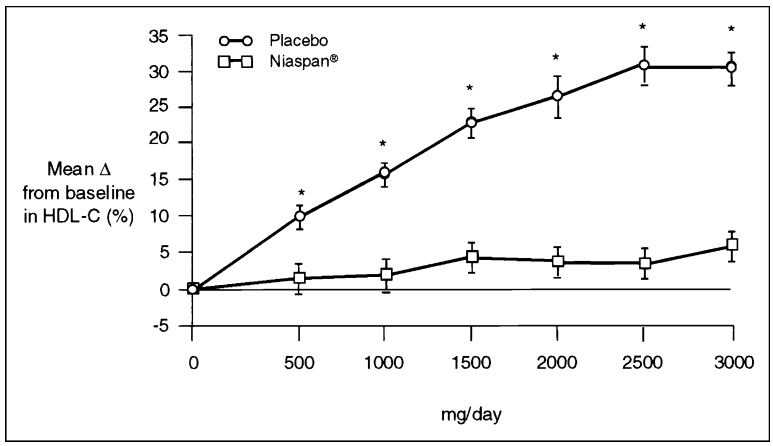

FIGURE 2. Mean percent change from baseline in HDL cholesterol. *p ≤0.05 versus placebo.

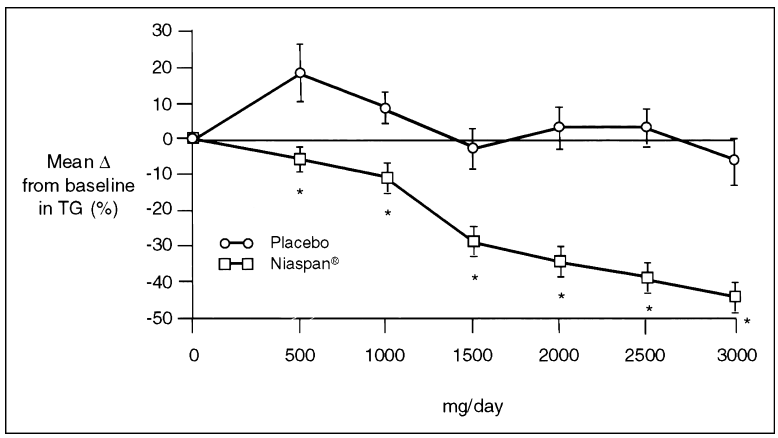

FIGURE 3. Mean percent change from baseline in triglycerides (TG). *p ≤0.05 versus placebo.

ness, nausea, vomiting, and diarrhea. Of the 26 patients discontinued from the extended-release niacin group, 8 were withdrawn while receiving 500 mg, 6 while receiving 1,000 mg, 4 while taking 1,500 mg, 3 while on 2,000 mg, 4 while on 2,500 mg, and 1 while on 3,000 mg.

Lipoprotein response: Extended-release niacin resulted in significant reduction from baseline at all treatment visits in both primary efficacy measures of LDL cholesterol and apolipoprotein B, beginning with the 500-mg/day dose and all subsequent doses ($p \leq 0.05$). Decreases in LDL cholesterol (Figure 1) were 3% at 500 mg, 9% at 1,000 mg, 14% at 1,500 mg, 17% at 2,000 mg, 22% at 2,500 mg, and 21% at 3,000 mg. No significant differences in mean percent change from baseline for LDL cholesterol occurred in the placebo group at any treatment visit. The analysis also indicated that the magnitude of the response to extended-release niacin for LDL cholesterol tended to plateau or diminish after a dose of 2,500 mg/day was achieved. Decreases in apolipoprotein B were 2% at 500 mg, 7% at 1,000 mg, 14% at 1,500 mg, 16% at 2,000 mg, 22% at 2,500 mg, and 20% at 3,000 mg ($p \leq 0.05$ vs placebo for all doses except 500 mg).

Significant changes from baseline were also noted for secondary efficacy parameters, including HDL cholesterol and triglycerides. For HDL cholesterol (Figure 2), significant increases from baseline were first apparent with the 500-mg/day dose and were consistent at all subsequent doses ($p \leq 0.05$). These increases were 10% at 500 mg, 15% at 1,000 mg, 22% at 1,500 mg, 26% at 2,000 mg, 30.0% at 2,500 mg, and 29.5% at 3,000 mg. The HDL cholesterol response plateaued at doses >2,500 mg/day.

Significant decreases from baseline for triglycerides (Figure 3) occurred with the 1,000-mg/day dose and were apparent at all subsequent doses ($p \leq 0.05$). Reductions in triglycerides were 5% at 500 mg, 11% at 1,000 mg, 28% at 1,500 mg, 35% at 2,000 mg, 39% at 2,500 mg, and 44% at 3,000 mg.

Values for other selected efficacy parameters at baseline compared with various treatment doses are summarized in Table II. Beginning with the 1,000-mg/day dose, extended-release niacin led to statistically significant changes from baseline in the following additional parameters: total cholesterol, VLDL, lipoprotein(a), HDL_2, apolipoprotein A-l, and total cholesterol/HDL cholesterol ($p \leq 0.05$).

Safety: The frequency of selected chemistry parameters most relevant to niacin therapy, including aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase, fasting blood

TABLE II Mean Percent Change from Baseline in Selected Parameters

	Placebo				Extended-Release Niacin			
	Baseline (mg/dl)	1,000 mg (% Δ)	2,000 mg (% Δ)	3,000 mg (% Δ)	Baseline (mg/dl)	1,000 mg (% Δ)	2,000 mg (% Δ)	3,000 mg (% Δ)
Total cholesterol	292	−1	—	−2	307	−5*	−12*	−16*
VLDL	40	9	2	−6	37	−11*	−35*	−45*
Lipoprotein(a)	34	−3	—	−5	43	−12*	−24*	−26*
HDL_2	6	8	19*	18*	6	38*	69*	72*
Apolipoprotein A-1	127	3	4*	4	132	8*	12*	12*
Total cholesterol/HDL cholesterol	7	−2	−2	−7*	7	−17*	−29*	−35*

*p ≤0.05 from baseline; p ≤0.05 for extended-release niacin versus placebo for all time points and parameters except lipoprotein(a) and apolipoprotein A-1 at 1,000 mg.

TABLE III Liver Enzyme Values and Mean Change from Baseline

	Aspartate Transferase (% change from baseline)		Alanine (% change from baseline)	
	Extended-Release Niacin	Placebo	Extended-Release Niacin	Placebo
Baseline	17	17	25	25
1,000 IU/L	18 (7)	18 (9)	24 (5)	25 (14)
2,000 IU/L	19 (12)*	16 (−6)	22 (−2)	23 (−2)
3,000 IU/L	21 (23)*	16 (−2)	24 (3)	23 (−4)

*p ≤0.05 from baseline.

sugar, uric acid, total bilirubin, amylase, and phosphorus, were not statistically different between the extended-release niacin and placebo groups when defined as 1.3 times, 2 times, and 3 times the upper limit of normal. There was a small but statistically significant increase in aspartate aminotransferase at the 2,000- and 3,000-IU/L doses of extended-release niacin, and no significant increase in alanine aminotransferase at any dose. Significantly more patients on extended-release niacin therapy experienced slightly above-normal elevations of uric acid, and slightly below-normal declines in phosphorus levels than those taking placebo (p ≤0.05). No patients exhibited elevations in fasting blood sugar >1.3 times the upper limit of normal. Significant differences in fasting blood sugar from baseline and compared with placebo were variable and did not appear to be dose-related. In the extended-release niacin group, mean fasting blood sugar at baseline increased by 3.5% at 500 mg, 5.4% at 1,000 mg, 5.0% at 1,500 mg, 1.8% at 2,000 mg, 5.7% at 2,500 mg, and decreased by 0.4% at 3,000 mg.

Table III shows the change from baseline in liver enzymes in the extended-release niacin and placebo groups. Extended-release niacin was not associated with any elevations >3 times the upper limit of normal in any chemistry parameter evaluated. Aspartate aminotransferase elevations >2 times the upper limit of normal occurred in 2 patients on extended-release niacin and 1 on placebo, a difference that was not statistically significant. For the remaining parameters, increases >1.3 times the upper limit of normal were observed for alanine aminotransferase, alkaline phosphatase, uric acid, and total bilirubin. Uric acid increased from an average baseline value of 5.3 to 7.0 mg/dl at the 3,000-mg dose. Phosphorus decreased from an average baseline value of 3.6 mg/dl to the lowest average treatment value of 3.0 mg/dl. Overall, changes in chemistry parameters among extended-release niacin-treated patients were significantly different from placebo only for uric acid and phosphorus.

No patient withdrew from extended-release niacin therapy because of abnormal laboratory values, compared with 1 placebo patient who was withdrawn early due to elevated liver tests.

Selected hematologic factors were also monitored. Of these, decreases in platelet count, which were first evident in the extended-release niacin group with the 1,000-mg dose (−8%) and continued at each subsequent dose (−11%, −13%, −14%, and −16%, respectively), were thought to be the most clinically relevant (p ≤0.05 vs baseline).

The number of patients who experienced episodes of flushing decreased with each extended-release niacin dose increment throughout the course of the study. At the 500-mg dose, 54 patients (68%) reported episodes of flushing. This figure dropped to 40 patients (58%) at the 1,000-mg dose, 25 patients (42%) at the 1,500-mg dose, 18 (33%) at the 2,000-mg dose, 11 (22%) at the 2,500-mg dose, and 10 (22%) at the 3,000-mg dose. Similarly, the mean number of flushing incidents per patient in the extended-release niacin group decreased through the 2,500-mg dose, with a slight but insignificant increase observed at the 3,000-mg dose. The mean incidence of flushing episodes per patient per month was highest (2.7) with the 500-mg dose, and decreased to 1.8 at the 1,000-mg dose, 1.4 at the 1,500-mg dose, 1.1 at the 2,000-mg dose, and 0.5 at the 2,500-mg dose. This figure increased slightly to 0.7 at the 3,000-mg dose. Flushing episodes decreased in mean intensity across visits to the 2,500-mg dose. Taken together, these data suggest that tolerance to flushing may develop with ongoing extended-release niacin therapy.

The most common adverse events reported in extended-release niacin and placebo patients, respectively, were headache (25% and 30%), abdominal pain (10% and 9%), diarrhea (28% and 23%), dyspepsia (11% and 14%), nausea (18% and 9%), vomiting (10% and 2%), pharyngitis (13% and 18%), rhinitis

(32% and 36%), pruritus (11% and 0%), and rash (10% and 0%). One patient in the placebo group died during the treatment phase of the study. Six other serious adverse events were reported during the study, 4 of which occurred among patients in the extended-release niacin group and 2 among patients in the placebo group. Three of the 4 serious adverse events in the extended-release niacin group were due to elective surgeries, as was 1 of the serious adverse events in the placebo group. The remaining patient on extended-release niacin experiencing a serious adverse event was hospitalized for a bilateral carotid endarterectomy 9 days after her study termination visit. The remaining patient on placebo experienced increased blood pressure, dizziness, and palpitations. Of the 7 patients experiencing serious adverse events, 1 patient on extended-release niacin and 1 on placebo completed the study. None of these events appeared to be related to study medications.

DISCUSSION

The efficacy and safety of this extended-release niacin formulation have been evaluated in several placebo-controlled, multicenter trials, which have demonstrated that, when administered at 1,000, 1,500, or 2,000 mg at bedtime, it significantly alters the lipid profile compared with placebo. For example, a trial of 122 patients with baseline LDL cholesterol levels $>$160 mg/dl and HDL cholesterol levels $\leq$70 mg/dl evaluated the safety and effectiveness of the 1,000- and 2,000-mg doses.[14] A dose-response efficacy profile was demonstrated for both parameters. A significant decrease from baseline was noted for LDL cholesterol, which was reduced by 6% and 14%, with the 1,000- and 2,000-mg doses, respectively. HDL cholesterol increased significantly, by 17% with the 1,000-mg dose and by 23% with the 2,000-mg dose. The 2,000-mg dose was also associated with significant decreases of 27% and 29%, respectively, for lipoprotein(a) and triglycerides. The trial demonstrated that extended-release niacin is associated with a favorable tolerability profile with no evidence of hepatic toxicity.

Mixed dyslipidemia is a significant risk factor for coronary heart disease events, with a high prevalence of low HDL cholesterol, hypertriglyceridemia, and/or elevated lipoprotein(a) levels, regardless of the LDL cholesterol level.[15] The risk profile in this study improved in several major areas, with mean reductions of up to 22% in LDL cholesterol, 22% in apolipoprotein B, and 44% in triglycerides, and increases of up to 30% in HDL cholesterol. For these reasons, the results support the effectiveness of extended-release niacin administered once daily at bedtime. The dose-response effects observed in this study demonstrate the smooth, consistent, linear effects of extended-release niacin throughout the recommended maintenance dosing range. Further, by improving a broad spectrum of lipid parameters, extended-release niacin has the potential to reduce the risk of primary and secondary coronary heart disease events. The overall magnitude of the response to extended-release niacin demonstrated a plateau of response above approximately 2,500 mg, particularly for LDL cholesterol, apolipoprotein B, lipoprotein(a), and total cholesterol/HDL cholesterol. The maximum recommended dose of extended-release niacin is 2,000 mg.

Niacin therapy has been associated with glucose intolerance, increased uric acid levels, and abnormal liver tests in patients taking daily doses of $\geq$500 mg of older sustained-release (or timed-release) niacin preparations.[2,10,16,17] A comparison of an older sustained-release and immediate-release niacin found that while the sustained-release form was significantly more effective than immediate-release niacin in lowering LDL cholesterol, its effects on HDL cholesterol were substantially less, and there was significant hepatotoxicity.[2] Hepatotoxic side effects of sustained release niacin were noted in 52% of patients.[2] No instances of hepatotoxicity were noted in those taking immediate-release niacin, although the formulation did result in transient liver function abnormalities. The current results indicate that the Niaspan extended-release formulation is at least as effective as immediate-release niacin and, for LDL cholesterol, sustained-release niacin with liver function results comparable to immediate-release niacin and superior to older sustained-release niacins. Another report has documented the occurrence of liver abnormalities upon switching from plain to time-released niacin.[10] In the present study, extended-release niacin was safe and efficacious, with a low incidence of liver enzyme abnormalities and an absence of withdrawals due to hepatotoxicity.

Analyses of alkaline phosphatase, lactate dehydrogenase, fasting blood sugar, uric acid, total bilirubin, amylase, and phosphorus revealed no unexpected adverse events. Liver tests were abnormal more often in those taking extended-release niacin than in patients taking placebo, but these elevations appeared to be reversible on discontinuation of study medication, and there was no evidence of irreversible liver toxicity or fulminant hepatotoxicity. Other biochemical changes were consistent with those previously reported for niacin. Nevertheless, patients receiving niacin (or other lipid-lowering medications) should be monitored periodically for clinical and biochemical changes in liver function.

Extended-release niacin was generally well tolerated. Only 8 patients discontinued active therapy due to flushing, which may have been due in part to the forced titration design of the study. The proportion of patients reporting flushing decreased across visits as the dose increased; again, this could be due in part to forced titration. The number of patients experiencing episodes of flushing decreased as the dose increased in a dose-response fashion through the 3,000-mg dose. There was a low incidence of adverse effects in patients treated with extended-release niacin that did not appear to be dose related, and most events overall were considered mild or moderate in severity.

Of the statistically significant changes in hematologic parameters observed during the study, only the difference in platelet count may be clinically relevant.

However, there were no apparent symptoms of bleeding or bruising in these patients.

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