

Treatment of Hypercholesterolemia: Comparison of Younger versus Older Patients Using Wax-Matrix Sustained-Release Niacin

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Objective: Compare lipid response, side effect profile and toxicity of younger (<50 years) versus older (50 to 70 years) hypercholesterolemic subjects taking wax-matrix sustained-release niacin (Endur-acin®).

Study Design: An 8-week randomized double-blind placebo controlled trial.

Setting: General community.

Participants: Volunteers from community cholesterol screening programs and chart review of patients at family practice clinics. Male and female subjects, age 20 to 70, with baseline low density lipoprotein cholesterol level within the 75th to 95th percentile, excluded if on medications that affect lipids or if a history of diabetes, gout, peptic disease, or liver disease is present.

Intervention: Nicotinic acid dosage schedules were 1,000 mg/day, 1,250 mg/day, 1,500 mg/day, or 2,000 mg/day for 8 weeks.

Main Outcome Measures: Change in blood lipids and blood

chemistries, side effects, and pill compliance.

Results: 158 subjects (79%) completed the study. Higher dose groups (1,500 mg and 2,000 mg) demonstrated improvements in total cholesterol, LDL-cholesterol, HDL cholesterol, and total-to-HDL-cholesterol ratio ($P < 0.05$) compared to baseline and controls. Higher-dose older subjects demonstrated significantly greater improvements than younger subjects on comparable doses for total cholesterol, HDL cholesterol, total-to-HDL-cholesterol ratio, and triglycerides, $P < 0.02$. Adherence to medication schedules was better and incidence of side effects and toxicity no greater in older subjects compared to younger.

Conclusion: Wax-matrix niacin (Endur-acin®) was shown to be effective and well tolerated for the pharmacological treatment of hypercholesterolemia. Older persons, ages 50 to 70, appear to experience greater benefits with no greater side effects when compared to younger subjects on similar doses. *J Am Geriatr Soc 40:12-18, 1991*

Recent analysis of the Framingham study indicates that dyslipidemia continues to be a significant cardiovascular risk factor into older age, at least to age 70.¹ In addition, high density lipoprotein cholesterol (HDL-C) was shown to be a strong independent risk factor in the elderly, especially in women with elevated triglycerides (TG).² The National Cholesterol Education Program guidelines recommend niacin as one of the "first choice" drugs when pharmacological treatment is indicated.³ Despite the well known problems with cutaneous and gastrointestinal side-effects, niacin has a long-standing experience of safety and efficacy and is modest in cost. Also, niacin typically reduces low density lipoprotein cholesterol (LDL-C) and TG while at the same time raising levels of HDL-C.⁴

The bioavailability of the wax-matrix form of sustained release niacin has been shown to be superior to a commonly prescribed capsule form of time-release niacin.⁵ An uncontrolled study using wax-matrix niacin reported good efficacy and a relatively low incidence of medication dropouts (4%) and side effects.⁶ The

clinical trial reported below was conducted to evaluate the efficacy and side effects of several dosage levels of wax-matrix niacin (Endur-acin®). In addition, the study was designed to assess the lipid response, tolerance, and side effect profile of younger subjects on this form of niacin as compared to older subjects.

METHODS

Recruitment Potential subjects were initially identified by chart review at two family practice training clinics and review of results from community-based cholesterol screening programs. Individuals were invited by letter to be screened for the study if they were between 20 and 70 years of age and had a previously recorded serum cholesterol between the 75th and 95th percentile for age and sex by Lipid Research Clinics Standards.⁷ The intention was to select subjects with hypercholesterolemia on a polygenic rather than a familial basis. Exclusionary conditions were the following: fasting triglyceride level greater than 400 mg/dL; fasting serum glucose greater than 140 mg/dL; hyperuricemia or history of gout; history of peptic ulcer disease; active liver disease; history of drug or alcohol abuse; concurrent use of drugs known to affect lipid levels including estrogens and oral contraceptives; previous surgical treatment to lower lipid levels; and pregnancy or a reasonable chance of becoming pregnant during the study. Subjects who qualified for the study

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on the basis of initial cholesterol and chemistry screening were further evaluated with two additional complete plasma lipid profiles (total cholesterol (TC), low density lipoprotein (LDL-C), high density lipoprotein (HDL-C), and triglycerides (TG)). Plasma specimens were used for lipid analysis throughout the study. Subjects gave written informed consent for this study which was approved by the Human Subjects Committee of the University of Minnesota.

Laboratory Methods All blood samples for lipid determinations were obtained using a standardized protocol for phlebotomy technique and specimen handling. Plasma specimens were frozen, batched, and then analyzed by the Clinical Chemistry Laboratory of the University of Minnesota Hospital, a CDC-certified facility for lipid analysis. Total and HDL cholesterol were measured with the cholesterol oxidase method using Roche Diagnostic Systems reagent and a Roche COBAS FARA analyzer. The HDL-C specimen was first precipitated with magnesium chloride and dextran sulfate.⁸ Triglycerides were assayed with an enzymatic method using Boehringer Mannheim Diagnostics reagent (Triglyceride GPO) and the Roche COBAS FARA analyzer. LDL cholesterol was calculated using the standard Friedewald formula.

Study Protocol All subjects underwent a complete health history and physical examination at study entry to note baseline physical findings and cardiovascular risk factors. An end of study physical exam was optional.

After initial enrollment, all participants received instruction in the American Heart Association Step I diet (AHA-I) consisting of a 2-hour small group lecture given by a registered dietitian. Participants were advised to continue with the AHA-I diet for the duration of the study. They were informed that dietary compliance would be monitored by unscheduled phone calls from certified interviewers near the end of each study phase.⁹

After a minimum of 6 weeks of dietary intervention, participants were randomized into treatment groups for the experimental phase of the study. Subjects were stratified by age, sex, and LDL-C level to ensure proportional distribution of these variables among seven study groups—diet alone, placebo (two groups), and niacin treatment (four groups). Niacin dosage varied among treatment groups and over time as depicted in Table 1. For this paper, the groups were analyzed by dividing subjects into older, 50 to 70 years in age ($n = 86$) and younger, 20 to 49 years in age ($n = 72$). Table 2 shows the comparison of younger and older groups by decade of age and sex. For comparisons, the seven study groups were also combined into a higher dose niacin group, 1,500 mg and 2,000 mg, lower dose niacin group, 1,000 mg and 1,250 mg, a combined placebo group, and a diet alone group. Thus, for each age group (younger and older) there were four com-

parison groups (high dose niacin, low dose niacin, placebo, and diet).

Niacin and placebo tablets were distributed at large group meetings conducted by the investigators. These meetings also served as patient education sessions. Niacin side effects were discussed, and means of handling common side effects were described (eg, taking niacin with food or preceded by an aspirin tablet to reduce the incidence of flushing). The importance of continuing the AHA-I diet was stressed.

Three fasting plasma lipid profiles on three separate days were obtained from every subject at entry, at the end of diet phase, and at the end of each of the three treatment phases: low dose (A), intermediate (B), and full dose (C). Three lipid determinations were made at each interval to enhance representativeness, and the mean of the three values was used for analysis.¹⁰ To monitor for blood chemistry changes, fasting chemistry profiles (including glucose, calcium, phosphorus, cholesterol-total, uric acid, urea nitrogen-BUN, creatinine, total protein, albumin, globulin, A/G ratio, bilirubin-total, alkaline phosphatase, AST, LDH) were obtained at entry and at the end of intermediate dose and full dose phases.

The Innovite Corporation, the producer of Enduracin, supplied both niacin and placebo tablets, which were identical in appearance and taste. Innovite also packaged the tablets according to a double blind scheme in which niacin and placebo groups were known to investigators and participants only by group number and color of label. The identity of treatment groups was kept in a locked safe until the completion of the study. No medical complications occurred to require breaking of the code.

Monitoring for Dietary and Drug Adherence Baseline dietary behavior was assessed by a self-administered semi-quantitative food frequency questionnaire.¹¹ To assess dietary adherence after initial group instruction by the registered dietitian, subjects were contacted by certified interviewers near the end of each study phase and asked to recall everything they had eaten in the preceding 24 hours. Food portion visual charts had been given to each patient so that they could accurately assess portion size. Information obtained from phone interviews was analyzed using the University of Minnesota Nutrition Coordinating Center's computerized diet analysis. Dietary behavior with respect to intake of cholesterol, saturated fats, and polyunsaturated fats was further analyzed using Keys' formulas to determine the impact of diet on plasma lipids.¹²⁻¹⁵

Compliance with drug regimens was estimated with pill counts. Subjects were informed that each pill bottle contained more pills than were actually required for each study phase; remaining pills were expected to be turned in at the end of each phase for counting.

Monitoring for Side Effects Side effects were

Table 1. SUMMARY OF PROTOCOL

Phase: Week: 0	Diet 6	A 10	B 18	C 24
Older Subjects (<i>n</i> = 86) (50–70 years old)				
Higher dose group (<i>n</i> = 21) (2000–1500 mg)	AHA-I	250	1500/1000	2000/1500
Lower dose group (<i>n</i> = 26) (1250–1000 mg)	Diet	250	750/500	1250/1000
Placebo (<i>n</i> = 26)		Placebo	Placebo	Placebo
Diet (<i>n</i> = 13)		Diet	Diet	Diet
Younger Subjects (<i>n</i> = 72) (20–40 years old)				
Higher dose group (<i>n</i> = 26) (2000–1500 mg)	AHA-I	250	1500/1000	2000/1500
Lower dose group (<i>n</i> = 26) (1250–1000 mg)	Diet	250	750/500	1250/1000
Placebo (<i>n</i> = 12)		Placebo	Placebo	Placebo
Diet (<i>n</i> = 8)		Diet	Diet	Diet

Table 2. COMPARISON OF AGE AND SEX OF YOUNGER AND OLDER GROUPS

Younger (<i>n</i> = 72)		Older (<i>n</i> = 86)	
	<i>n</i> (%)		<i>n</i> (%)
Males	59 (71.4)	Males	47 (54.2)
Females	22 (28.6)	Females	39 (45.8)
Age		Age	
20–29	7 (4.4)	50–59	45 (28.5)
30–39	24 (15.2)	60–70	41 (25.9)
40–49	41 (25.9)		
Mean age = 39.9		Mean age = 58.7	

evaluated by questionnaire at the end of appropriate study phases. Niacin's common side effects (flushing, GI upset, pruritis) and less common side effects (dizziness, diarrhea, palpitations, visual changes) were listed, and participants were asked to report any new incidence and change in frequency or intensity of these and any other symptoms experienced. Frequency of side effects was estimated, and severity of side effects was rated on five-point Likert scales. In addition, because side effects could be an important factor affecting dropout rate, any participants who failed to complete the study were contacted by phone and asked to give their reasons for discontinuation.

Statistical Analysis Analysis of repeated measures was used to compare treatment groups with respect to desired improvement in lipid profiles. For significant group by phase interactions, post-hoc analyses were accomplished using Tukey's HSD test to investigate group differences at specific phases. Chi-square and Fisher's Exact tests were used for analysis of categorical variables and student's *t* tests for analysis of continuous variables. One way ANOVAS were used to investigate group differences in nutritional variables at the beginning of the study and at the end of each phase. A cut-off level of $P < 0.05$ (two-sided) was utilized for assessing statistical significance.

RESULTS

Two-hundred one subjects were randomized into the study groups as described above. One-hundred fifty-eight subjects (79%) completed the entire study protocol. Of the 43 who did not complete, 24 cited logistical problems such as work, clinic scheduling difficulties, transportation problems, and child care conflicts. Others dropped out primarily for medical reasons unrelated to the study or had moved out of the area during the study. Of the 117 subjects assigned to niacin treatment groups, four dropped out due to presumed niacin side effects, resulting in a 3.4% niacin-related dropout rate. Of the four who discontinued the study due to intolerance of niacin, one was on 750 mg dosage, 2 were on 1,500 mg, and one was on 2,000 mg. The side effects which caused the intolerance were flushing and tingling for the persons on 750 mg and one of those on 1,500 mg and gastrointestinal upset for the person on 2,000 mg and the other on 1,500 mg. Of note, none of the dropouts (mean age 36, range 27 to 44) were in the older group.

Changes in Lipid and Lipoprotein Values Group means were obtained at the end of each study phase for TC, LDL-C, HDL-C, TC/HDL-C, and TG. Table 3 summarizes the results of the plasma lipid parameters for the higher dose and placebo groups by study phase.

The entire study group demonstrated a modest improvement in lipid values during the diet phase. They averaged a 2.7% decrease in TC, a 3.3% decrease in LDL-C, a 2% decrease in TC/HDL-C, and no change in HDL-C and TG. There were no significant differences in lipid results between younger subjects and older subjects in the diet phase and no significant lipoprotein responses between male and female subjects throughout the study.

Lipid Changes in Older Subjects By the end of Phase C, among the older subjects, the higher dose (HO) niacin treatment group had experienced a significant improvement ($P < 0.01$) from baseline levels in TC (–22%), LDL-C (–29%), HDL-C (+8%), TG (–21%), and TC/HDL-C (–25%). The improvements

Table 3. SUMMARY OF LIPID RESULTS BY PHASE PERCENT CHANGE FROM BASELINE TO PHASE C AND DIET TO PHASE C

	Baseline	Diet	Phase A	Phase B	Phase C	% Δ Base to C	% Δ Diet to C
Cholesterol							
Older 2000/1500 ^{ac}	280 \pm 21	268 \pm 34	267 \pm 24	246 \pm 38	219 \pm 51	-22†	-18†
Younger 2000/1500 ^{ac}	254 \pm 15	245 \pm 25	245 \pm 24	227 \pm 28	227 \pm 20	-11	-7
Older placebo ^a	269 \pm 18	269 \pm 23	267 \pm 26	268 \pm 21	261 \pm 22	-3	-3
Younger placebo ^b	240 \pm 24	224 \pm 37	227 \pm 28	226 \pm 34	223 \pm 32	-7	-0.4
LDL-C							
Older 2000/1500 ^{ac}	195 \pm 17	185 \pm 28	186 \pm 22	161 \pm 33	138 \pm 47	-29†	-25†
Younger 2000/1500 ^{ac}	177 \pm 15	167 \pm 23	169 \pm 22	153 \pm 22	148 \pm 19	-16	-11
Older placebo ^b	186 \pm 15	185 \pm 22	182 \pm 24	187 \pm 22	178 \pm 21	-4	-4
Younger placebo	170 \pm 19	156 \pm 31	159 \pm 23	158 \pm 27	154 \pm 27	-9	-0.4
HDL-C							
Older 2000/1500 ^{bc}	50 \pm 11	48 \pm 12	49 \pm 12	54 \pm 16	54 \pm 15	+8	+13
Younger 2000/1500 ^{bc}	46 \pm 10	45 \pm 11	47 \pm 11	47 \pm 12	49 \pm 10	+7	+9
Older placebo	53 \pm 16	54 \pm 16	55 \pm 17	54 \pm 15	54 \pm 15	+2	0
Younger placebo	46 \pm 12	45 \pm 12	46 \pm 10	47 \pm 10	45 \pm 12	-2	0
TG							
Older 2000/1500 ^{ac}	173 \pm 55	175 \pm 61	160 \pm 61	155 \pm 74	136 \pm 57	-21	-22
Younger 2000/1500	155 \pm 70	158 \pm 81	155 \pm 104	144 \pm 87	156 \pm 94	+0.6	-1
Older placebo	148 \pm 50	146 \pm 59	151 \pm 60	137 \pm 49	144 \pm 51	-2	-1
Younger placebo	119 \pm 58	114 \pm 42	107 \pm 46	108 \pm 37	121 \pm 53	+2	+6
TC/HDL-C							
Older 2000/1500 ^{ac}	5.9 \pm 1.2	5.8 \pm 1.1	5.7 \pm 1.1	4.8 \pm 1.4	4.4 \pm 1.6	-25§	-24§
Younger 2000/1500 ^{ac}	5.8 \pm 1.5	5.7 \pm 1.6	5.6 \pm 1.5	5.2 \pm 1.6	4.9 \pm 1.4	-16	-14
Older placebo ^a	5.5 \pm 1.7	5.4 \pm 1.7	5.3 \pm 1.6	5.4 \pm 1.5	5.2 \pm 1.3	-5	-4
Younger placebo	5.6 \pm 1.5	5.3 \pm 1.4	5.1 \pm 1.1	5.0 \pm 1.2	5.1 \pm 0.9	-9	-4

^a Change significant ($P < 0.01$) from Baseline to Phase C.

^b Change significant ($P < 0.05$) from Baseline to Phase C.

^c Change significant ($P < 0.01$) from Diet to Phase C.

^d Change significant ($P < 0.05$) from Diet to Phase C.

† Change significant ($P < 0.05$) compared to all other groups.

§ Change significant ($P < 0.05$) compared to all other groups except younger high dose.

Not all significant differences labeled.

in lipids (TC, LDL-C, HDL-C, TG, and TC/HDL-C) in the HO group at the end of Phase C were also significant ($P < 0.05$) when compared to their lipid results after the diet phase. Further, the improvement in all lipid parameters in the HO group from baseline to phase C and end of diet phase to phase C was significantly ($P < 0.05$) greater than those seen in the other older groups (lower dose, placebo, and diet).

Lipid Changes in Younger Subjects Among younger subjects, by the end of Phase C, the higher dose group (HY) showed significant reductions ($P < 0.05$) in TC (-11%), LDL-C (-16%), HDL-C (+7%) and TC/HDL-C (-14%) in comparison to their baseline lipid levels. These lipid changes were also significant ($P < 0.05$) when compared to the end of diet phase levels and to diet controls at the end of phase C but not in comparison to placebo or lower dose groups.

Younger vs Older When comparing lipid changes from baseline to the end of Phase C in the higher dose groups (HO and HY), the HO demonstrated significantly greater reductions ($P < 0.02$) of TC, LDL-C, TC/

HDL-C, and TG. However, HDL-C changes were not significantly different between the HO and HY.

Adherence to AHA-I Diet and Medication Regimen Adherence to the AHA-I diet as monitored by 24-hour diet recall phone contacts showed all groups maintained close to the prescribed diet. There were no significant differences between groups with respect to parameters of the AHA-I diet. Weight remained stable in all groups or demonstrated slight loss due to restricted fat intake.

In all phases, the overall pill compliance for all groups was greater than 90% of scheduled doses. Differences between groups were not significant, but older subjects had somewhat better compliance than younger subjects in all groups.

Monitoring of Serum Chemistries Fasting serum chemistries obtained at entry and after Phase B and C of the study indicated no significant increase in mean values for all groups (young and old) for the following tests: total calcium, uric acid, blood urea nitrogen, total protein, albumin, globulin, albumin/globulin, and bil-

Table 4. SUMMARY OF BLOOD CHEMISTRY VALUES BY PHASE CHANGE FROM BASELINE TO PHASE C

	Baseline	Phase B	Phase C	Change from Baseline to end of Phase C
Glucose (mg/dL)				
Older 2000/1500	100 ± 8.6	106 ± 7.8	106 ± 12	+6
Younger 2000/1500	100 ± 9.8	102 ± 10	104 ± 12	+4
Older placebo	104 ± 15	101 ± 13	104 ± 15	0
Younger placebo	96.7 ± 9.1	96.7 ± 10	96.1 ± 11	-0.6
Alkaline Phosphatase (AP) (U/L)				
Older 2000/1500	84.9 ± 18.4	93.5 ± 26.4	108 ± 48.0	+23.1
Younger 2000/1500	74.0 ± 21.3	77.8 ± 21.8	83.5 ± 23.3	+9.5
Older placebo	80.7 ± 23.8	78.2 ± 22.9	78.7 ± 22.2	-2.0
Younger placebo	72.7 ± 29.3	75.7 ± 30.3	75.8 ± 24.2	+3.1
Aspartate Aminotransferase (AST) (U/L)				
Older 2000/1500	20.9 ± 5.4	24.4 ± 8.4	33.4 ± 23.8	+12.5
Younger 2000/1500	22.1 ± 8.7	21.9 ± 6.9	23.3 ± 11.8	+1.2
Older placebo	21.8 ± 6.1	20.0 ± 5.7	20.5 ± 6.6	-1.3
Younger placebo	23.9 ± 8.0	27.0 ± 13.4	28.7 ± 15.4	+4.8
Lactate Dehydrogenase (LDH) (U/L)				
Older 2000/1500	139 ± 22.7	165 ± 23.6	177 ± 25.7	+38
Younger 2000/1500	135 ± 17.3	154 ± 23.9	162 ± 21.2	+27
Older placebo	146 ± 19.5	154 ± 24.1	159 ± 19.7	+13
Younger placebo	142 ± 30.7	165 ± 35.6	166 ± 32.1	+24

irubin. However, the mean test results (summarized in Table 4) for serum glucose, alkaline phosphatase (AP), aspartate amino-transferase (AST), and lactate dehydrogenase (LDH) tended to rise with increased niacin dosage in the high dose groups (both young and old). The group means for these tests were all within normal limits. Abnormal serum chemistry results, in general, occurred with comparable frequency in the control groups and the niacin treatment groups. Elevated AP was not significantly more common in the niacin groups (5%) when compared to the control groups (3%) at the end of Phase C. Abnormal AST results were slightly more frequent in control groups (7%) than in niacin treated groups (4%). Abnormal serum glucose elevations were more common among all older subjects (18%) than younger (4%), but AST abnormalities were more common among younger subjects (9%) than older (2%). Increases in AST, LDH, and AP had a strong inverse correlation with decrease in LDL-C ($r = 0.46$ for AST, $r = 0.32$ for LDH, $r = 0.31$ for AP, $P < 0.0001$ for all) in niacin treated subjects.

Side Effects The side effect questionnaire asked subjects to report the incidence and severity of any new symptoms since the beginning of the study or increased incidence or severity of existing symptoms that had occurred during the study phase in question. The majority of older and younger subjects on niacin experienced some new symptoms presumed to be due to the medication; these were generally quite manageable or transient. In essentially every symptom category, older subjects reported less frequent new incidence of side effects. Further, when side effects were rated for clinical importance in terms of severity and

frequency, older subjects reported no greater incidence of "clinically significant" problems with side effects than younger subjects (Table 5).

DISCUSSION

Lipoprotein Changes The 79% completion rate and relatively high compliance of subjects to diet and medication schedules reflected good cooperation of participants and allowed meaningful comparisons among groups. The significantly greater improvement in plasma TC, LDL-C, TC/HDL-C, and TG seen in older patients when compared to younger on comparable doses of niacin was a completely unexpected finding. This age difference in responsiveness to niacin has not been previously described. Both older and younger subjects were comparably adherent to medication and diet regimens so the difference does not appear to be artifact. Of note, both older and younger subjects demonstrated similar improvements in HDL-C. This supports the suggestion by Knapp that the niacin mechanism of action on HDL-C metabolism is different than that on LDL-C.¹⁶ Apparently the niacin-HDL-C pathway is not significantly changed by age.

The exact mechanisms of action of niacin on lipid metabolism is not known. One of the pharmacological actions of niacin is believed to be a lipolytic inhibition in fatty tissues resulting in decreased delivery of non-esterified fatty acids to the liver.¹⁷ This, in turn, results in decreased hepatic synthesis of triglycerides and a subsequent decline in the production of very low density lipoproteins (VLDL-C). Since VLDL-C is a precursor of LDL-C, this sequence results in the lowering of LDL-C. The VLDL-C fraction of cholesterol was not

TABLE 5. INCIDENCE OF SIDE EFFECTS EXPERIENCED BY NIACIN-TREATED SUBJECTS (ALL DOSES)

Symptom	Younger		Older	
	% Incidence	Clinically Significant*	% Incidence	Clinically Significant*
Flushing	80	14	77	16
Itching	66	12	55	9
Tingling	56	10***	39	0
Upper GI Symptoms	44**	12	23	5
Constipation	14	2	14	2
Diarrhea	24	4	22	9
Dizziness**	28	0	7	5
Palpitations	14	2	7	2
Blurred Vision	16	2	14	2

* Clinically significant is defined as any side effect at any incidence (even once) that was rated by subjects as moderate or greater in intensity.

** Reported incidence of side effect significantly ($P < 0.05$) less in Older than Younger subjects.

*** Reported incidence of clinically significant side effect significantly ($P < 0.05$) less in Older than Younger subjects.

measured in this study, so, unfortunately, there is no direct assessment of this fraction. Niacin also appears to have a direct inhibition of hepatic synthesis of cholesterol by decreasing HMG-CoA reductase activity.¹⁷ Since niacin's mechanism of action on lipid metabolism is not known, it is difficult to even speculate on the reasons why older persons seem more responsive than younger, at least, in the areas of LDL-C and TG metabolism.

Biochemistry Changes An interesting and potentially important finding for the clinical management of niacin therapy is an observation resulting from the serum chemistry monitoring. An increase in the enzyme levels of AST, LDH, and AP correlated strongly and significantly with the reduction in LDL-C in all niacin treatment groups, whereas the control groups failed to demonstrate such a correlation. These findings support an hepatic site of action for niacin's lipid lowering effect. Of note, older subjects, who as a group demonstrated greater LDL-C reductions, also showed a greater mean rise in enzyme levels (AST, LDH, AP). The increase in enzyme levels for the great majority of subjects remained within the range of normal for these tests, yet it is unclear whether this is indicative of a therapeutic response or incipient toxicity. These subjects were on their highest dose of niacin for only 8 weeks. Thus, it was not certain that their liver function had yet stabilized on that level of medication. Longer term follow-up with monitoring is needed.

It should be noted that sustained-release niacin has been implicated in several reports as causing a drug induced toxic hepatitis.¹⁸⁻²⁰ This hepatitis reaction appears to be, at least in part, idiosyncratic rather than strictly dose related and can occur at relatively modest doses of niacin. One subject in this study developed abdominal pain, nausea, vomiting, and moderate elevation of AST (177 IU/L). It is important that subjects on niacin, especially sustained release, be monitored by physicians and have periodic serum chemistries. The fact that abnormal elevations of AST occurred even more frequently in controls than niacin-treated subjects should also alert physicians that these changes

may be due to other causes. Physicians managing niacin therapy may want to re-check borderline abnormalities before discontinuing niacin.

Impaired glucose tolerance and the potential adverse effects of the resultant hyperinsulinemia have been described in subjects treated with nicotinic acid.^{21,22} This appears to be particularly a concern in the case of non-insulin dependent diabetics when treated with nicotinic acid.²¹ Even though subjects in this study did not manifest serious deterioration in glucose metabolism, this parameter should be monitored in clinical settings.

Bioavailability Other studies have not specifically looked at response differences to niacin by age, but response differences by formulation (sustained-release versus unmodified niacin) have been described.¹⁶ It is apparent that there are wide differences in bioavailability, side effects, and lipid responses to the various formulations of niacin.^{5,6,23} Sustained-release formulations of niacin have been developed to reduce the incidence of side effects, but unfortunately some products seem to accomplish this by reduced absorption and bioavailability. Wax-matrix niacin has been shown to have equivalent bioavailability on a milligram for milligram basis to unmodified niacin.⁵ The results described in this paper can and should be attributed only to the wax-matrix form of sustained release niacin (Endur-acin) that is the only form of niacin with this type of sustained release delivery system. Physicians and patients alike should be cautioned that various sustained release niacin products are not comparable despite equivalent milligram strength.

Niacin Tolerance and Side Effects The common cutaneous and gastrointestinal side effects usually seen with niacin therapy were experienced, at least transiently, by many of the niacin-treated subjects. But, of importance clinically, these symptoms were reported overwhelmingly as mild, infrequent, or self-resolving. Of note, in most side effect categories, younger subjects reported more frequent or as frequent incidence as older subjects.

Perhaps the best clinical measure of tolerance is the dropout rate (3.4%) due to drug-related side effects. Studies using other forms of sustained release niacin have reported a 16% to 40% drop out rate due to drug intolerance.^{16,23} In this study, all niacin-related dropouts were from the younger group. This apparent better tolerance of niacin by older subjects was unexpected and even ironic in that niacin has a notorious reputation for side effects, and older patients, as a group, tend to be more sensitive to drug side effects. The adherence to medication regimens by niacin-treated subjects (87%–91%) also suggests that wax-matrix niacin is well tolerated.

CONCLUSION

This study supports consideration of wax-matrix sustained-release niacin when pharmacological treatment of hypercholesterolemia is indicated. Niacin has long had a positive record for safety and efficacy and has a desirable effect on HDL-C and TG as well as LDL-C. Significant lipid improvements can be obtained on moderate doses of wax-matrix niacin with acceptable rates of intolerance (3.4%) and frequency of significant side effects (0%–16%).

Although subjects in this study were on niacin for 20 weeks, only the final 8 weeks were at full dosage. Further research is needed to confirm that the results of this study can be sustained over a longer period and that long-term safety, especially with respect to potential liver toxicity, and tolerance can be maintained. In addition, this study raises intriguing questions regarding the cause of age differences in response to niacin and the actual mechanisms niacin influences on hepatic synthesis of cholesterol. Further study is needed of these issues and the possible use of liver enzyme changes within the normal range to monitor and predict optimal therapy.

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