A Clinical Trial of Oat Bran and Niacin in the Treatment of Hyperlipidemia

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Background. Previous studies have demonstrated the lipid-lowering potential of wax-matrix controlled-release forms of nicotinic acid, but questions have been raised about the risks associated with long-term use. This report describes a 38-week trial that was designed as a follow-up to a shorter 16-week clinical trial of wax-matrix controlled-release niacin. The present study also tested the hypothesis that niacin (1500 mg/d) and oat bran (56 g/d [2 oz/day]) may have a synergistic effect on improving serum lipid levels.

Methods. Ninety-eight subjects began the following protocol: oat bran alone (6 weeks), oat bran plus niacin (6 weeks), and niacin alone (32 weeks). Blood lipids, blood chemistries, nutritional variables, and side-effect profiles were monitored throughout the study. Sixty-nine (70%) subjects completed the trial taking the full dose of niacin (1500 mg/d); 8 subjects completed the trial taking a reduced dose of niacin (average 906 mg/d); 11 discontinued taking any niacin because of either intolerable side effects (n = 7) or liver enzyme abnormalities (n = 4).

Results. Generally, oat bran–niacin synergism was not found. Only 10% of subjects who completed the study showed greater than expected lipid improvement on combination therapy. From baseline to the end of the final phase, significant reductions ($P < .05$) occurred for total cholesterol (−10%) and low-density lipoprotein cholesterol (−16%). High-density lipoprotein cholesterol rose significantly at the end of the oat bran plus niacin phase, but returned to near baseline by the end of the study. The liver enzymes alkaline phosphatase, lactate dehydrogenase, and aspartate aminotransferase all showed a tendency to rise throughout the study.

Conclusions. The results of this 38-week trial suggest that the relatively inexpensive wax-matrix form of niacin is effective and reasonably well tolerated. Approximately 8% of subjects were unable to continue taking niacin because of side effects, and 4% discontinued taking niacin because of liver enzyme elevations. A small group of subjects (10%) experienced greater than expected lipid improvements (synergism) on combined oat-bran and niacin therapy. Liver function monitoring with long-term use of niacin is warranted.

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Recent studies using a wax-matrix form of controlled-release nicotinic acid (CNA) (Endur-acin) have suggested improved clinical potential for this particular formulation of nicotinic acid, and invite a reexamination of the risks vs the benefits of CNA.[1,2] Wax-matrix CNA has bioavailability comparable to unmodified nicotinic acid.[3] Recently, we reported a randomized controlled clinical trial of wax-matrix CNA (201 subjects) demonstrating efficacy (−19% to −26% change in low-density lipoprotein [LDL] cholesterol as a result of taking 1500 to 2000 mg/d) with a low incidence of intolerance (3.7%).[2] Trials using other (non–wax-matrix) CNA products have typically reported drug intolerance due to side effects in the range of 16% to 40% of subjects.[4,5]

The above studies suggest that wax-matrix CNA may offer desirable clinical advantages over unmodified nicotinic acid and other forms of CNA. These studies have not resolved the issue of drug safety with the use of wax-matrix CNA, however, especially with respect to the potential for hepatotoxicity. In the clinical trial cited above, the reduction in LDL cholesterol was associated with a modest but significant rise for the highest dose group (2000 mg) in baseline levels of liver enzymes.[2] The study was relatively short in duration, only 8 weeks at full

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dose. It raised but did not answer the question of whether the liver enzyme changes observed (though generally within the normal range for those blood chemistries) were evidence of therapeutic effect or incipient liver toxicity.

To answer that and related longer term efficacy and tolerance questions, a 38-week sequel study at a stable dosing level (1500 mg) with repeated interval blood lipid and chemistry determinations was undertaken. A total daily dose of 1500 mg of wax-matrix CNA was determined from the previous clinical trial to be optimal for most persons.

In addition, wax-matrix CNA had been reported anecdotally to be more effective for cholesterol management when used in conjunction with a fat-modified diet and oat bran supplement. The sequel study was designed to also evaluate this potential synergistic effect of oat-bran supplement with wax-matrix CNA.

Methods

Study Subjects

Of the 158 subjects completing the initial clinical trial of wax-matrix CNA, 98 agreed to participate in the sequel study. There was a 4-month interval between the completion of the clinical trial and the beginning of the sequel study, effectively accomplishing a washout of niacin effects between the studies. Originally, subjects had been recruited from community cholesterol screening programs, newspaper notices, and chart reviews of patients from two family practice training clinics. Men and women between 20 and 70 years of age with LDL cholesterol levels in the 75th to 95th percentile level for age and sex were included in the study. Individuals were excluded if they had a fasting triglyceride level >4.5 mmol/L(400 mg/dL), fasting glucose level >7.8 mmol/L (140 mg/dL), hyperuricemia, active liver disease, were presently using drugs that affect lipids, were pregnant or had a reasonable chance of becoming pregnant, had a history of gout, peptic ulcer disease, drug or alcohol abuse, or had surgical treatment to lower lipids.

Comparison of characteristics between the group of sequel study subjects and those in the original study revealed no apparent selection bias in the sequel study. Age was the only variable in which the two groups differed significantly (sequel study, 52 years, vs original study, 46 years, $P < .05$).

Laboratory Methods

All blood samples for lipid determinations in both the initial clinical trial and the sequel study were obtained using a standardized protocol for phlebotomy technique and specimen handling. Plasma specimens were used for all lipid analysis. The methods used for specimen handling and analysis have been detailed previously.[2]

Study Protocol

The study design was a sequential trial of all subjects consuming oat bran alone, followed by oat bran with wax-matrix CNA, and finally wax-matrix CNA alone. The study was conducted in three phases: Phase 1 was a 6-week treatment period using the American Heart Association Step I (AHA-1) diet supplemented with 28 g (1 oz) twice daily of instant hot oat bran cereal. Phase 2 was also 6 weeks in length, with the treatment consisting of 1500 mg/d of wax-matrix CNA added to the initial treatment of AHA-1 diet and oat bran (56 g [2 oz]). Phase 3 was a 32-week period (with lipid and chemistry monitoring at midpoint, ie, week 16) consisting of the AHA-1 diet and wax-matrix CNA (1500 mg) without the oat-bran supplement. Subjects were given a choice of taking either 500-mg or 750-mg tablets to enhance overall compliance with taking pills during the sequel study.

Lipid profiles were obtained at baseline and at the end of each phase. Three different fasting morning samples were collected on separate (usually consecutive) days, and the average of the three samples was used in data analysis. Blood chemistry testing was also done on fasting samples obtained at baseline, at the end of phase 2, and at the midpoint and end of phase 3. The Innovite Corporation (Tigard, Ore) supplied the 750-mg and 500-mg wax matrix CNA tablets in prelabeled bottles, and Quaker Oats Company (Barrington, Ill) supplied the instant hot oat bran cereal in premeasured 28-g (1-oz) packets.

Monitoring for Dietary and Drug Adherence

Baseline dietary behavior was assessed by a self-administered, semiquantitative food frequency questionnaire.[6] To assess dietary adherence during the study, 4-day food records were completed during each phase. Subjects were requested to keep their diet adjustments isocaloric as much as possible for the study period and not to intentionally change lifestyle or physical activity in a manner that might independently affect their weight and lipids. Compliance with drug regimens was estimated with pill counts. Actual pill counts were compared with expected counts to determine the percentage of compliance with doses.

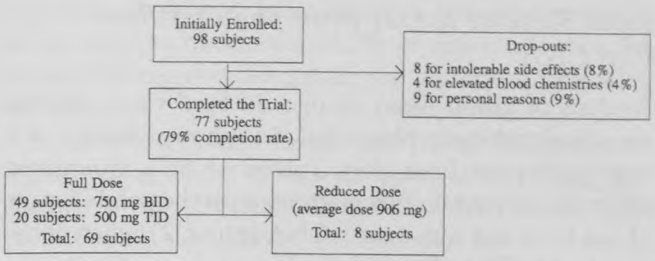

Figure 1. Description of 98 subjects and treatment regimens in a trial using niacin to reduce cholesterol.

Monitoring for Side Effects

Side effects were evaluated by questionnaire at the end of study phases 2 and 3. The common side effects of niacin (flushing, gastrointestinal upset, pruritis) and less common side effects (dizziness, diarrhea, palpitations, visual changes) were listed, and participants were asked to report new incidence or change in frequency and severity of these and any other symptoms experienced. Severity of side effects was rated on 5-point Likert scales (1 = never, 2 = rarely, 3 = occasionally, 4 = frequently, 5 = very frequently).

Statistical Analysis

For blood lipids, blood chemistries, and nutritional variables, repeated-measures analysis of variance was used to determine overall significance. Between-phase significant differences were assessed by the use of two-tailed paired *t* tests. For each blood lipid value, 95% confidence intervals were constructed around the mean difference from baseline to the end of the study. For the side-effects data, two-tailed paired *t* tests were used to assess changes by phase.

Results

Subjects

Figure 1 shows the various dispositions of the 98 subjects who entered the study including those who dropped out. Subjects who had developed niacin-related side effects or blood chemistry elevations were given the option of either dropping out of the study or attempting to remain in the study on a reduced dose. Of the total group of 20 subjects experiencing either intolerance or blood chemistry elevations at the 1500-mg level, 8 elected to continue at a lower dose. All 8 of these subjects successfully completed the 44 weeks at a reduced dose (250 to 1250 mg/d), which resulted in the resolution of abnormal blood chemistries and side effects.

Lipoproteins

Table 1 summarizes lipoprotein changes by study phase for full-dose (1500 mg) subjects. Of note, there was no significant mean change in lipids during the first 6-week treatment phase of the AHA-1 diet and 56 g of daily oat bran. Significant ($P < .05$) reductions in total cholesterol (−10%), LDL cholesterol (−14%), and ratio of total cholesterol to HDL cholesterol (−8%) were demonstrated between the baseline levels of these lipids and the end of phase 2 after the addition of 1500 mg of wax-matrix CNA to the oat bran and AHA diet. These sig-

Table 1. Lipid Values* by Study Phase, Significant Differences, and 95% Confidence Intervals

Lipid	Preliminary (PRE)	End Cereal-Only Phase (6 wk) (CO)	End Cereal + Niacin Phase (6 wk) (CN)	End Niacin-Only Phase (32 wk) (NO)	Significant Differences	Mean Difference and 95% CI,† Preliminary to End of Niacin-Only Phase mmol/L (mg/dL)
Total cholesterol	6.5 ± 0.61 (250 ± 23.7)	6.5 ± 0.72 (250 ± 27.9)	5.8 ± 0.76 (226 ± 29.5)	5.8 ± 0.71 (224 ± 27.6)	PRE v CN, NO = P ≤ .001	−0.67 (−26) −0.84, −0.50 (−33, −20)
LDL cholesterol	4.4 ± 0.61 (172 ± 23.5)	4.4 ± 0.63 (171 ± 24.2)	3.8 ± 0.68 (148 ± 26.3)	3.7 ± 0.62 (145 ± 24.0)	PRE v CN, NO = P ≤ .001	−0.71 (−27) −0.89, −0.53 (−34, −21)
HDL cholesterol	1.3 ± 0.33 (49.7 ± 12.8)	1.3 ± 0.34 (49.6 ± 13.0)	1.3 ± 0.43 (50.6 ± 16.6)	1.3 ± 0.36 (49.3 ± 14.1)	NS	+0.01 (+0.40) −0.03, 0.06 (−1.4, 2.2)
Total cholesterol/HDL cholesterol ratio	5.3 ± 1.4	5.4 ± 1.4	4.9 ± 1.5	4.9 ± 1.4	PRE v CN, NO = P ≤ .001	−0.40 −0.69, −0.24
Triglycerides	1.6 ± 0.61 (143 ± 53.6)	1.6 ± 0.77 (144 ± 68.1)	1.6 ± 0.75 (141 ± 66.2)	1.7 ± 0.71 (149 ± 62.8)	NS	0.07 (+6.0) −0.06, 0.2 (−5.7, 17.8)

**Lipid values in mmol/L (mg/dL); mean ± SD.*
†95% confidence intervals that include 0 are not significant at the .05 level; narrow, significant intervals suggest greater precision of the value.

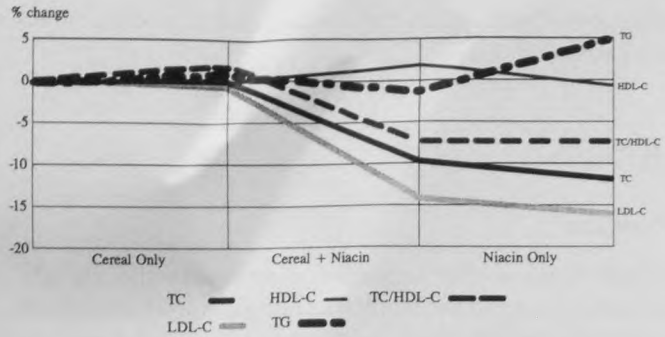

Figure 2. Percent change in lipid values by study phase in 77 subjects receiving cereal only, then cereal and niacin, and then niacin only. TC denotes total cholesterol; HDL-C, high-density lipoprotein cholesterol; TC/HDL-C, ratio of total cholesterol to HDL-cholesterol; LDL-C, low-density lipoprotein cholesterol; and TG, triglycerides.

nificant ($P < .05$) reductions from baseline were maintained through the 32 weeks of phase 3. There was no significant change from baseline in HDL cholesterol or triglycerides throughout the study. Figure 2 shows graphically the percentage of change from baseline of lipid values by study phase.

Lipid Changes in the Reduced CNA Dosage (250 to 1250 mg/d) Group

The eight subjects who completed the study taking a reduced dose of niacin demonstrated a significant ($P < .05$) reduction from baseline in total cholesterol (−12%), LDL cholesterol (−22%), and ratio of total cholesterol to HDL cholesterol (−20%) when lipid levels were measured at the end of phase 2, while subjects were still taking the full dose (1500 mg/d). The lipid levels of those taking the reduced dose (average 906 mg/d) rose somewhat, but at the end of phase 3 (total cholesterol −9%, LDL cholesterol −16%, and ratio of total cholesterol to HDL cholesterol −16%) the lipid levels remained essentially comparable to those of subjects in the higher dose groups. The reduced-dose subjects demonstrated greater improvements in HDL cholesterol (+13%) and triglycerides (−12%) than the full-dose subjects over the course of the study, but because of the small size of the group, these changes were not statistically significant. One subject took only 250 mg of wax-matrix CNA per day, yet still demonstrated beneficial lipid improvements (LDL cholesterol −29%; HDL cholesterol +15%; triglycerides −20%). Of note, the reduced-dose subject group had a significantly lower mean body weight than the full-dose subject group (71.4 kg vs 81.4 kg $P < .05$).

Lipid Response to Oat Bran and Oat Bran Plus CNA

Analysis of group mean changes in lipid values during the sequential study phases failed to show evidence of a response to oat bran alone (phase 1) or a synergistic effect for the overall subject group with the combination of oat bran and wax-matrix CNA (phase 2) when compared with CNA alone (phase 3).

Analysis of individual lipid responses by phase identified 10% of subjects (n = 7) who demonstrated a greater reduction (possible synergism) in LDL cholesterol when taking the combination of oat bran and niacin than could be explained by the additive effects of each treatment alone. The mean values for changes from baseline in LDL cholesterol in this subgroup were: phase 1 (oat bran) −4%; phase 2 (oat bran–niacin combination) −27%; phase 3 (niacin-only phase) −11%. There were no unique subject or baseline characteristics identified that could differentiate this subgroup from the overall group.

Serum Chemistries

For subjects who completed the study taking the full dose (1500 mg), uric acid and bilirubin did not change significantly throughout the study. Serum glucose increased significantly ($P < .05$) from baseline to phase 2, but then returned by phase 3 to a level not significantly different from baseline. The liver enzymes alkaline phosphatase (AP), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH) all demonstrated a tendency to rise over the course of the study. The AST values were observed to rise by 2 or more standard deviations (AST, SD = ±7.2 U/L) from the baseline level to the end of the study in six subjects (8%). For three subjects this represented an abnormal elevation of AST (normal range 0 to 50 U/L). Overall, eight subjects had a change in at least one liver function enzyme (AP, AST, LDH) greater than 2 standard deviations above the baseline mean. As a group, these eight subjects had an average reduction in LDL cholesterol of 26% (range −17% to −42%) suggesting a correlation between lipid reduction and liver function enzymes.

CNA Side Effects and Pill Compliance

Intolerance of side effects caused eight subjects to withdraw from the study, three because of flushing and cutaneous symptoms, three because of gastrointestinal upset symptoms, and two because of headaches. Overall, compliance with the niacin treatment phases was 93% of doses as judged by pill counts. Compliance was compa-

rable in both groups: those to whom 500 mg three times daily was prescribed took 93.7% of doses, and those to whom 750 mg two times daily was prescribed took 92% of doses.

Common cutaneous side effects (eg, flushing, itching, tingling of the skin) were rated as occurring "frequently to very frequently" by 8% of subjects, and gastrointestinal side effects (ie, nausea, upset stomach, heartburn) were rated as occurring "frequently to very frequently" by 6% of subjects.

Adherence to AHA-1 Diet and Oat Bran Side Effects

Adherence to the AHA-1 diet was monitored by 4-day food records during each of the study phases. The average percentage of total calories derived from fat was 31.5%. The mean daily intake of cholesterol for the three study phases was 208 mg, and the means for percentage of total calories from saturated, monounsaturated, and polyunsaturated fat were 9.6%, 11.9%, and 7.6%, respectively.

Discussion

Sixty-nine (70%) subjects completed the study taking the full dose of niacin, and demonstrated good compliance with medication regimens throughout the study (over 93% of scheduled doses), allowing meaningful comparisons of study phases. Of particular interest, subjects who had developed elevated liver enzyme levels or symptoms of intolerance while taking the 1500-mg dose level of CNA demonstrated prompt (within 3 weeks) resolution of those problems with reduction of dose (8 subjects) or discontinuance of the CNA (12 subjects). Overall, these findings were consistent with the older literature on nicotinic acid that has regarded liver enzyme changes as relatively benign and generally easily managed with a reduction or discontinuation of the drug.[7]

A disquieting finding was the slight gradual increase in the group mean level of the liver enzyme AST over the 38 weeks of receiving CNA therapy, suggesting that even at stable dosages, continued long-term monitoring of liver function is necessary. Parsons,[7] in his review of the effect of niacin on the liver, described AST as the most useful and sensitive enzyme with which to monitor liver function. Parsons has conducted perhaps the most extensive study of the effect of nicotinic acid on the liver, including biopsies on subjects who have developed abnormal enzyme levels. He noted that liver function abnormalities are more common with the use of controlled-release niacin preparations, but liver biopsy findings were not supportive of drug-induced hepatitis. Further, he believed that the prompt resolution of abnormalities argued against liver toxicity. He concluded that nicotinic acid causes a "functional alteration of enzymatic reactions without hepatocellular damage."[7]

More recent reports, however, have raised concern regarding CNA-induced toxic hepatitis. Two series of cases report liver enzyme (AST) levels in the range of 2 to 100 times normal on a variety of sustained-release preparations.[8,9] In each case, liver function tests returned to normal, usually within a few days to a few weeks after the discontinuance of CNA. Persistent or permanent liver problems were not suspected, so liver biopsies were not obtained. A more dramatic case report, however, described fulminant hepatic failure requiring a liver transplant in a person who had switched from unmodified nicotinic acid to 6 g of CNA (not wax-matrix CNA) for only 3 days.[10] These cases highlight the fact that severe liver toxicity can occur and indicate a need for appropriate caution and monitoring with the use of CNA. Perhaps such findings ultimately argue for prescription control of the use of niacin as a lipid-lowering agent.

One subject was advised to discontinue the study because of persistent elevation of serum glucose. Worsening of glucose tolerance in diabetic subjects taking niacin has been reported, so persistent glucose elevation is clearly an indication to discontinue niacin.[11] Other blood chemistry abnormalities were not a problem in this study. There were no elevations of uric acid or bilirubin, and the rise in the mean serum glucose level in phase 2 appeared to self-resolve over the longer niacin phases 3 and 4.

Side Effects and Intolerance

The 8.2% dropout rate due to symptomatic drug intolerance is higher than that reported from previous studies with wax-matrix CNA[1,2] but is still considerably lower than reports from studies using other forms of CNA (16% to 40%).[4,5] An additional 6% to 8% of subjects reported tolerable but frequent cutaneous or gastrointestinal symptoms. These subjects would have likely benefited from a dosage adjustment if this had been an actual clinical practice setting. On average, the subjects requiring a reduction in dose weighed 10 kg less than individuals on the full dose (1500 mg/d). Thus, it would appear clinically prudent to start with lower doses in smaller persons.

Of possible clinical interest, the dosage schedule of 500 mg three times per day vs 750 mg twice daily for the same daily intake (1500 mg) appeared to change the side-effects profile. Gastrointestinal side effects were less frequent with the larger dose twice daily, while cutane-

ous side effects were reduced by spreading the total daily intake over three doses. Though these differences were statistically significant, the subjects were not randomized to dosage schedules, so these findings may be subject to selection bias.

Lipid Response and Niacin–Oat Bran Synergism

Both oat bran and wax-matrix CNA have independently been demonstrated to significantly reduce cholesterol in previous well-controlled studies.[2,12] Because of fixed dosage schedules and lack of control groups, this study was not designed to optimally assess efficacy. However, the sequence of interventions—oat bran alone, oat bran plus wax-matrix CNA, and wax-matrix CNA alone—was intended to allow comparisons in the same group of subjects on each of the three treatment options. Background eating behavior, as monitored by 4-day food records, was stable throughout the study period and there was no more than a 2% mean weight change for the entire study.

The lipid response in phase 1 was less than expected and it appeared that 56 g (2 oz) of oat bran supplement had virtually no effect on blood lipids. The LDL cholesterol response during phase 1 (oat bran alone) ranged from an increase of 75% to a reduction of 48%, and the overall group was equally divided between postive and negative responses. In an attempt to look for oat bran–niacin synergism, the data were analyzed to identify subjects who had demonstrated a reduction of LDL cholesterol that was greater when they were taking the combination of oat bran and wax-matrix CNA (phase 2) than the sum of LDL cholesterol response when taking oat bran (phase 1) and wax-matrix CNA independently (LDL cholesterol response for phase 3). Seven subjects had a lipid response that could be considered suggestive of a synergistic effect from the combination of oat bran and niacin. Thus, the enhanced lipid response to the combination of oat bran and niacin was not sufficiently prevalent to support a general hypothesis of synergism. Up to 10% of persons, however, might experience a greater than expected added benefit from combined therapy.

The overall lipid response was as anticipated for total cholesterol and LDL cholesterol, but the HDL cholesterol and triglyceride changes were less than expected. Niacin in general and wax-matrix CNA in particular have been shown in other studies to raise HDL cholesterol and lower triglycerides.[1,2] Knopp et al[4] have hypothesized that there are two separate niacin mechanisms of action on cholesterol. One action raises HDL cholesterol and seems to be more effective at lower doses (about 1000 mg/d), while a second lowers LDL cholesterol and increases in effect with increasing dose. Interestingly, the subjects on the reduced-dose regimen in this study demonstrated a better HDL cholesterol response (+13%) than did the full-dose (1500 mg) subjects (−0.6%). The clinical trial using wax-matrix CNA that preceded this sequel study supported the theory of Knopp et al; but in that study, the 1500-mg dose of wax-matrix CNA gave a better HDL cholesterol (+9%) and triglyceride (−8%) response than seen in this sequel.[4]

Though useful for summarizing a study, the reporting of results as group mean data obscures individual differences in response. What is evident from this and other studies of wax-matrix CNA is the considerable individual variation in response that underscores the need for clinical monitoring and individual titration for the optimal dose. An advantage of the apparent dual mechanism of action of niacin on lipids is the potential for treating isolated low HDL cholesterol dyslipidemia with a considerably lower dose of niacin. Likewise, clinicians should be aware that as they titrate the dose up to improve LDL cholesterol and triglyceride response, they may see some decrease in the beneficial effect on HDL cholesterol. In this study lipid response and tolerance appeared to be quite individual, although body mass did show a relationship to tolerance. The study demonstrated that patients who develop signs of intolerance or toxicity can be successfully managed with continued benefit to lipids by lowering the daily dose.

Conclusions

This study, and previous research, suggest that wax-matrix CNA offers substantial clinical advantages over other forms of nicotinic acid. The study protocol's fixed-dose wax-matrix CNA (1500 mg) resulted in a 16% reduction of LDL cholesterol and was relatively well tolerated over an extended treatment period of 38 weeks. In actual clinical practice, titration of the dose for optimal lipid response and tolerance could be expected to yield even better results. At an average cost of 25 cents per day, this offers clinicians and patients a pharmacological intervention that is significantly less expensive than most of the effective alternative drugs (one fifth to one tenth of the cost). Although asymptomatic elevations of liver enzymes did occur, they returned to normal within 3 weeks or less after lowering the dosage or discontinuing the drug.

The continued rise in AST levels over the study duration underscores an important caveat: the therapeutic effect of wax-matrix CNA must be balanced with its potential for hepatotoxicity. Likewise, long-term monitoring of blood chemistries (especially AST), even with

stable dosing, is recommended. Finally, wax-matrix CNA did not generally show evidence of lipid-lowering synergism when used with a 56-g/d supplement of instant hot oat bran. However, some subjects did experience greater than expected lipid improvements on combined therapy.

Acknowledgments

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References

1. Alderman JD, Pasternak RC, Sacks FM, Smith HS, Monrad ES, Grossman W. Effect of a modified, well-tolerated niacin regimen on serum total cholesterol, high density lipoprotein cholesterol and the cholesterol to high density lipoprotein ratio. Am J Cardiol 1989; 64:725–9.
2. Keenan JM, Fontaine PL, Wenz JB, Myers S, Huang Z, Ripsin C. Niacin revisited: a randomized, controlled trial of wax-matrix sustained-release niacin in hypercholesterolemia. Arch Intern Med 1991; 151:1424–32.
3. Figge HL, Figge J, Souney PF, et al. Comparison of excretion of nicotinuric acid after ingestion of two controlled release nicotinic acid preparations in man. J Clin Pharmacol 1988; 28:1136–40.
4. Knopp RH, Ginsberg J, Albers JJ, et al. Contrasting effects of unmodified and time-release forms of niacin on lipoproteins in hyperlipidemic subjects: clues to mechanism of action of niacin. Metabolism 1985; 34:642–50.
5. Luria MH. Effect of low-dose niacin on high-density lipoprotein cholesterol and total cholesterol/high-density lipoprotein cholesterol ratio. Arch Intern Med 1988; 148:2493–5.
6. Willett WC, Reynolds RD, Cottrell-Hoehner S, Sampson L, Browne ML. Validation of a semi-quantitative food frequency questionnaire: comparison with a 1-year diet record. J Am Diet Assoc 1987; 87:43–7.
7. Parsons WB. The effect of nicotinic acid on the liver. Evidence favoring functional alteration of enzymatic reactions without hepatocellular damage. In: Altschul R, ed. Niacin in vascular disorders and hyperlipidemia. Springfield, Ill: Charles C Thomas, 1964.
8. Etchason JA, Miller TD, Squires RW, et al. Niacin-induced hepatitis: a potential side effect with low-dose time-release niacin. Mayo Clin Proc 1991; 66:23–8.
9. Henkin Y, Johnson KC, Segrest JP. Rechallenge with crystalline niacin after drug-induced hepatitis from sustained-release niacin. JAMA 1990; 264:241–3.
10. Mullen GE, Greenson JK, Mitchell MC. Fulminant hepatic failure after ingestion of sustained-release nicotinic acid. Ann Intern Med 1989; 111:253–5.
11. Garg A, Grundy SM. Nicotinic acid as therapy for dyslipidemia in non–insulin-dependent diabetes mellitus. JAMA 1990; 264: 723–6.
12. Davidson MH, Dugan LD, Buins JH, Bova J, Story K, Drennan KB. The hypocholesterolemic effects of beta-glucan in oatmeal and oat bran: a dose controlled study. JAMA 1991; 265:1833–9.