# A Comparison of the Efficacy and Toxic Effects of Sustained- vs Immediate-Release Niacin in Hypercholesterolemic Patients

James M. McKenney, PharmD; Jack D. Proctor, MD; Scott Harris, PharmD; Vernon M. Chinchili, PhD

**Objective.**—To compare escalating doses of immediate-release (IR) and sustained-release (SR) niacin for effectiveness in reducing levels of low-density lipoprotein cholesterol and triglycerides and increasing levels of high-density lipoprotein cholesterol, and for the occurrence of adverse reactions, especially hepatotoxicity.

**Design.**—Randomized, double-blind, parallel comparison of IR and SR niacin administered sequentially at 500, 1000, 1500, 2000, and 3000 mg/d, each for 6 weeks.

**Setting.**—Cholesterol research center.

**Patients.**—Forty-six adults, 23 in each group, with low-density lipoprotein cholesterol levels greater than 4.14 mmol/L (160 mg/dL) after 1 month of a step 1 National Cholesterol Education Program diet.

**Outcome Measures.**—Fourteen-hour fasting lipid and lipoprotein cholesterol levels, results of clinical laboratory tests, a symptom questionnaire, and withdrawal rates.

**Results.**—The SR niacin lowered low-density lipoprotein cholesterol levels significantly more than IR niacin did at the dosage of 1500 mg/d and above, while IR niacin increased high-density lipoprotein cholesterol levels significantly more than SR niacin did at all dosage levels. The reduction in triglyceride levels was similar with IR and SR niacin. Nine (39%) of the 23 patients assigned to the IR dosage form withdrew before completing the 3000-mg daily dose; the most common reasons for withdrawal were vasodilatory symptoms, fatigue, and acanthosis nigricans. Eighteen (78%) of the 23 patients assigned to the SR dosage form withdrew before completing the 3000-mg daily dose; the most common reasons for withdrawal were gastrointestinal tract symptoms, fatigue, and increases in levels of liver aminotransferases, often with symptoms of hepatic dysfunction. None of the patients taking IR niacin developed hepatoxic effects, while 12 (52%) of the 23 patients taking SR niacin did.

**Conclusion.**—The SR form of niacin is hepatotoxic and should be restricted from use. The IR niacin is preferred for the management of hypercholesterolemia but can also cause significant adverse effects and should be given only to patients who can be carefully monitored by experienced health professionals.

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ACCORDING TO the National Cholesterol Education Program, nicotinic acid is one of the primary drugs for treating hypercholesterolemia.[1] In daily doses of 2 to 3 g, it reduces total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels an average of 20% to 30%, lowers triglyceride levels 35% to 55%, and increases high-density lipoprotein cholesterol (HDL-C) levels 20% to 35%.[2-5] It also reduces levels of small, dense LDL-C and Lp(a) lipoprotein, both of which are associated with increased risk of coronary heart disease (CHD).[6,7] It is effective in the treatment of hypercholesterolemia, as well as mixed hyperlipidemia and hypoalphalipoproteinemia.[8-10] It has been shown to reduce total and CHD mortality when used in primary prevention[11] and to slow or reverse the progression of atherosclerosis when used with bile acid resins in secondary prevention.[11-15] It is widely available as an over-the-counter product and is one of the least expensive drugs for the management of dyslipidemia.

**For editorial comment, see p 709.**

Despite these numerous advantages, nicotinic acid has several notable disadvantages, mostly relating to its toxic effects. It is generally not well tolerated by patients, causing vasodilatory side effects in up to 100% of patients, particularly when administered in an immediate-release (IR) dosage form.[2,3] In clinical trials, about 25% of patients have to discontinue niacin use because of these symptoms.[3,16,17] Sustained-release (SR) dosage forms of nicotinic acid have been recommended to reduce vasodilatory side effects. Unfortunately, they are more likely to produce gastrointestinal tract side effects and may be less effective in lowering LDL-C levels and increasing HDL-C levels.[2,3] More importantly, there have been numerous case reports of hepatotoxic effects associated with SR niacin.[18-31]

This study was conducted to compare SR and IR niacin directly in a well-designed clinical trial. The objective was to compare escalating doses of IR and SR niacin for efficacy in reducing LDL-C and triglyceride levels and increasing HDL-C levels and for the occurrence of adverse effects as reflected by bothersome symptoms, changes in results of laboratory tests for blood glucose or liver function, and withdrawals from the study.

## PATIENTS AND METHODS

### Patient Selection

The study protocol was approved by the institutional review board, and a consent form was signed by each patient.

From the Schools of Pharmacy (Dr McKenney) and Medicine (Dr Proctor), Medical College of Virginia, Virginia Commonwealth University, Richmond; Baptist Medical Center, Little Rock, Ark (Dr Harris); and College of Medicine, Pennsylvania State University, Hershey (Dr Chinchili).

Reprint requests to PO Box 533, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA 23298 (Dr McKenney).

Adults with a history of high blood cholesterol levels were recruited by means of advertisements in the local newspaper and were taught the National Cholesterol Education Program saturated fat- and cholesterol-restricted step 1 diet by a registered dietitian.[1] Those who had LDL-C levels greater than 4.14 mmol/L (160 mg/dL) after following this diet for at least 1 month were eligible for the study. Patients were excluded if they had major medical problems; familial lipid disorders; secondary causes of hypercholesterolemia, including hypothyroidism, obesity (>140% of ideal body weight), diabetes mellitus, and renal disease; abnormal liver function; triglyceride levels greater than 9.05 mmol/L; or contraindications to niacin therapy, including active peptic ulcer disease; or if they were receiving drugs that could alter cholesterol levels. Patients whose conditions were stable with a fixed dose of antihypertensive or thyroid replacement medication, or conjugated estrogens for longer than 6 months, could participate if they maintained the same dose throughout the study. Patients were required to discontinue other cholesterol-lowering drug therapy 4 weeks before beginning the diet lead-in phase.

### Study Design

This was a randomized, double-blind, parallel-group study. It lasted 36 weeks and consisted of a 6-week lead-in period followed by five 6-week treatment periods. During the lead-in period, a medical history was taken and clinical laboratory tests and a physical examination were performed. Compliance with the diet was established by evaluating the patient's diary of all foods consumed for 3 days with a food record rating (FRR) score, a scoring system that roughly quantifies the saturated fat content in the diet.[32] Patients who obtained an FRR score of 15 or less at the end of the lead-in period were judged to be following a National Cholesterol Education Program step 1 diet. This diet was continued throughout the study and monitored by the use of 3-day diet diaries and FRR scoring at the end of each treatment period.

Patients were randomly assigned to receive IR niacin (Rugby Laboratories, West Hempstead, NY) or SR niacin (Goldline Laboratories, Ft Lauderdale, Fla). The drug was administered twice daily in identical-appearing capsules. During the first treatment period, patients took 250 mg/d for 1 week, followed by 500 mg/d for 5 weeks. Thereafter, the following dosages were sequentially introduced, and the patient took each one for 6 weeks: 1000, 1500, 2000, and 3000 mg/d. Dosages were escalated even if no increase was required for control of the patient's cholesterol level.

Table 1.—Mean Global Score and Percentage of Patients Who Reported at Least Moderately Bothersome Adverse Symptoms While Taking Escalating Doses of Immediate- or Sustained-Release Niacin

| Niacin Daily Dose, mg | No. of Patients | Global Score | % of Patients | | |
|---|---|---|---|---|---|
| | | | Vasodilatory Symptoms* | GI Tract Symptoms† | Fatigue |
| Immediate release | | | | | |
| Baseline | 23 | 3.8 | 22 | 22 | 4 |
| 500 | 23 | 6.6‡ | 48 | 26 | 4 |
| 1000 | 19 | 6.7‡ | 53 | 26 | 11 |
| 1500 | 19 | 7.9‡ | 32 | 32 | 21 |
| 2000 | 18 | 8.1‡ | 39 | 39 | 22 |
| 3000 | 14 | 6.3‡ | 29 | 14 | 14 |
| Sustained release | | | | | |
| Baseline | 23 | 2.9 | 22 | 26 | 7 |
| 500 | 23 | 3.2 | 13 | 22 | 4 |
| 1000 | 23 | 5.1 | 22 | 13 | 17 |
| 1500 | 21 | 4.5 | 19 | 13 | 19 |
| 2000 | 18 | 4.7 | 17 | 17 | 11 |
| 3000 | 9 | 7.1‡ | 22 | 56 | 33 |

*Flushing, tingling, headache, warmth, itching.
†GI indicates gastrointestinal. Nausea, gas, heartburn, diarrhea.
‡$P<.01$ vs baseline.

All patients were taught how to recognize and ameliorate side effects and adjust doses. Patients were advised to take an adult aspirin tablet 30 minutes before the morning niacin dose and to take each dose with food to minimize adverse effects.

### Study Measurements

Two 14-hour fasting blood samples for lipid and lipoprotein cholesterol measurements were obtained in all six study periods, one at the end of the fourth and another at the end of the sixth week. During the lead-in period, the average of these values was used to qualify patients for the study and to establish baseline levels. During each treatment period, the average of these values served as the measure of drug effect. If the patient was withdrawn from the study during any treatment period, any lipid values obtained were included in the efficacy analysis. Lipid results were available to the investigators throughout the study for use in encouraging patient compliance.

At the end of each study period, the occurrence of adverse effects was determined by use of patient history, clinical laboratory tests, and a symptom questionnaire. Patients were encouraged to report adverse effects at any time. If the adverse effect was clinically significant, the patient was withdrawn from the study. If it was not clinically significant, the patient was asked to reduce the niacin dosage to the previously tolerated dosage for 1 week and then to resume the scheduled dosage. If the adverse effect persisted or recurred, the patient was withdrawn from the study. Patients were always withdrawn when the results of liver function tests were greater than three times the upper limit of normal.

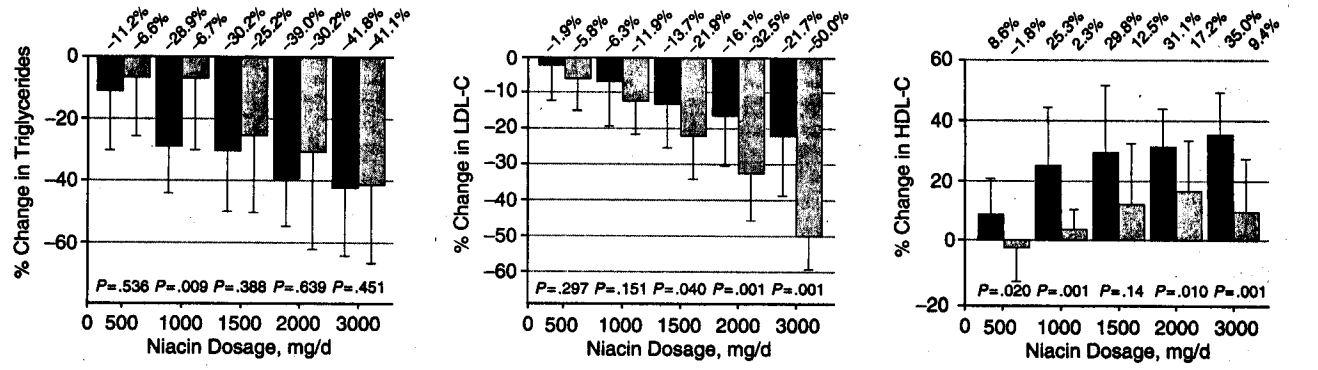
The symptom questionnaire contained a list of 11 symptoms commonly reported with niacin therapy (ie, vasodilatory symptoms of flushing, tingling, warm feeling, headache, rash, and itching; gastrointestinal tract symptoms of nausea, gas, heartburn, and diarrhea; and fatigue). For each symptom, patients were asked to indicate how bothersome the symptom had been during the previous 6 weeks. The patient's responses were converted to numeric scores by assigning 0 to 4 for least to most bothersome. A global score for each patient was determined at the end of each treatment period by adding the numeric scores of each symptom. The global score provided an estimate of the overall adverse effects associated with niacin therapy; it did not indicate that all adverse effects were of equal significance.

Compliance with niacin therapy was assessed by a capsule count at the end of each treatment period.

The laboratory used for this study was standardized by participation in the Centers for Disease Control Lipid Standardization Program. All analytes met Centers for Disease Control requirements for accuracy and precision.[33] Total cholesterol and triglyceride levels were measured enzymatically.[34] For the HDL-C determination, plasma was fractionated with 0.092-mol/L manganese chloride plus 183-U/L heparin solution followed by centrifugation, and the supernatant fraction was assayed for cholesterol.[35] The very-low-density lipoprotein cholesterol and LDL-C levels were calculated by the Friedewald formula applied to the measured values.[36]

### Statistical Methods

The minimum sample size estimation at a power $(1-\beta)$ of 90% and $\alpha=.05$ for




Mean percentage change (with SD) in triglycerides (left), low-density lipoprotein cholesterol (LDL-C) (center), and high-density lipoprotein cholesterol (HDL-C) (right) levels with immediate-release (darker bars) and sustained-release (lighter bars) niacin as dosage was increased from 500 to 3000 mg/d. Baseline levels were as follows: triglyceride, 2.11±1.02 mmol/L in the immediate-release group and 1.96±0.84 mmol/L in the sustained-release group; LDL-C, 5.24±0.73 mmol/L (202.8±28.6 mg/dL) in the immediate-release group and 5.20±0.59 mmol/L (201.1±22.8 mg/dL) in the sustained-release group; and HDL-C, 1.15±0.32 mmol/L (44.3±12.2 mg/dL) in the immediate-release group and 1.28±9.49 mmol/L (49.6±15.6 mg/dL) in the sustained-release group. Baseline values for immediate-release and sustained-release niacin were not significantly different for triglycerides ($P$=.251) or LDL-C ($P$=.775) by $t$ test. Baseline HDL-C values for immediate-release and sustained-release niacin were significantly different ($P$=.002) by $t$ test. $P$ values for cumulative changes in lipids and lipoproteins from baseline between immediate-release and sustained-release niacin are given in insert with each daily dosage (determined by repeated-measures analysis of variance).

a two-arm parallel study with two-tailed testing to detect a difference of 0.65 mmol/L (25 mg/dL) in LDL-C level with an SD of 0.67 mmol/L (26 mg/dL) was 23 for each group. The sample size required to determine a 0.23-mmol/L (9-mg/dL) difference in HDL-C level with an SD of 0.23 mmol/L (9 mg/dL) was 21 for each group.[36]

Efficacy analyses were performed by the Statistical Analysis System. A repeated-measures analysis of variance (ANOVA) was conducted for each of the following response variables: total cholesterol, triglyceride, LDL-C, very-low-density lipoprotein cholesterol, HDL-C, glucose, uric acid, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase levels; and global adverse symptom score. The treatment groups were unbalanced because of patient withdrawals; therefore, the restricted maximum likelihood estimation method described by Jennrich and Schluchter[37] was applied. The model consisted of terms for each patient's baseline mean and terms for mean changes from baseline for each period for each dosage form; the correlation structure within each patient was modeled as a general autoregressive process. From the results of the repeated-measures ANOVA, approximate $t$ tests were constructed for comparing the dosage forms within each period. For the lipid and lipoprotein cholesterol variables, measurements were taken at the end of weeks 4 and 6 of each period, so preliminary repeated-measures ANOVAs were performed on the differences between the two measurements to determine whether it was legitimate to average the values from these 2 weeks. All the calculations for the repeated-measures ANOVAs were performed in PROC MIXED of SAS 6.07.

Pearson's partial correlations among the lipid and lipoprotein cholesterol responses and alanine and aspartate aminotransferase levels were calculated for each dosage form. Partial correlations were used to adjust for the repeated measurements over dosage level for each dosage form. Exact $t$ tests were constructed to test that the partial correlations were significantly different from zero, and Fisher's $z$-transformation was applied to construct approximate 95% confidence intervals.[38] All such calculations were performed by the multivariate ANOVA statement in PROC GLM of SAS 6.07.

The period of a patient's last visit before withdrawal (last visit if the patient did not withdraw) was analyzed by means of ordinal logistic regression in which the regressor represented the difference between the two dosage forms. This was performed in PROC LOGISTIC of SAS 6.07. Also, the rate of withdrawals with the two dosage forms was compared by means of a likelihood-ratio $\chi^2$ test.

## RESULTS

### Study Patients

Fifty patients met the inclusion criteria; four patients were subsequently withdrawn because they required medical procedures that disrupted niacin therapy or were not compliant with the protocol. The remaining 46 patients, including 24 men and 22 women, of whom 32 were white and 14 black, were enrolled into the study.

Of these 46 patients, 23 were randomized to each treatment group. The mean (±SD) ages of patients in the IR and SR groups were 55.0±10.8 years and 52.0±10.4 years, respectively. Approximately half of the patients in each group were female and 35% were black. Patients in each group had from zero to four risk factors for CHD; family history, male sex, hypertension, and smoking were the most prevalent risk factors present. None of the patients had a history of CHD. The mean (±SD) baseline weight for patients in the IR group was 80.6±15.0 kg, and for patients in the SR group, it was 81.4±10.5 kg. The mean baseline values for LDL cholesterol and triglycerides were similar ($P$=.851 and .251, respectively), but the mean baseline HDL-C levels were different ($P$=.002) (Figure).

Compliance with the National Cholesterol Education Program diet and niacin regimens was acceptable throughout the study. The mean baseline FRR score was 8.8 (range, 3 to 15) in both groups. Mean FRR scores ranged between 9.0 and 11.2 during treatment periods and were not different between the IR and SR niacin groups. Individual scores greater than 15 were encountered in only 14 (7%) of the 208 individual patient diaries analyzed, and these scores decreased to less than 15 on reinforcement counseling. Patients took an average of 92% to 98% of prescribed niacin doses during the study's five treatment periods. Capsule counts were not different during any treatment period. Only 10 (7%) of 140 individual patients took less than 80% of prescribed doses during any one treatment period; these patients returned to acceptable levels after counseling by the investigator.

### Efficacy

Total cholesterol level was reduced by 1.5%, 4.8%, 9.8%, 11.1%, and 15.9% with IR niacin and by 5.6%, 9.0%, 17.0%, 24.7%, and 40.2% with SR niacin as dosages were

increased from 500 mg/d to 1000, 1500, 2000, and 3000 mg/d, respectively. Mean percentage changes in LDL-C, triglyceride, and HDL-C levels with escalating doses of IR and SR niacin are presented in the Figure. The reduction in triglyceride levels was similar with IR and SR niacin; a significant difference between the dosage forms was detected only at the dosage of 1000 mg/d.

The SR niacin lowered LDL-C levels significantly more than did IR niacin at dosages of 1500 mg/d and higher (Figure). The 1500-mg SR niacin dose and the 3000-mg IR niacin dose produced similar reductions in LDL-C levels (21.9% and 21.7%, respectively). At 1500 mg daily, SR niacin reduced LDL-C level in all 21 patients who received it (range, −3.1% to −50.0%), whereas IR reduced it in 17 of 19 patients (range, +13.3% to −40.2%). At 1500, 2000, and 3000 mg/d, IR niacin lowered LDL-C levels to less than 4.14 mmol/L (160 mg/dL), a common goal of therapy, in seven (39%) of 19 patients, nine (50%) of 18 patients, and nine (64%) of 14 patients, respectively. The use of SR niacin achieved this outcome in 12 (57%) of 21 patients, 14 (78%) of 18 patients, and nine (100%) of nine patients, respectively. For SR niacin, there was a significant correlation between the decrease in LDL-C level and the decrease in triglyceride level ($r$=.40, $P$=.001); the decrease in LDL-C and triglyceride levels with IR niacin was not significantly correlated ($r$=−.04, $P$=.772). Similar to the reduction in LDL-C level, total cholesterol levels decreased 2%, 5%, 10%, 11%, and 16% with IR niacin and 5%, 9%, 17%, 25%, and 39% with SR niacin as doses were increased.

The use of IR niacin increased HDL-C level significantly more than did SR niacin at all dosages (Figure). The increase with IR niacin was a substantial 25% at 1000 mg/d and 35% with 3000 mg/d. The dosage of 1000 mg/d of IR niacin increased HDL-C level in all 23 patients (range, 5.6% to 89%), while SR niacin increased it in only 15 of the 23 patients (range, −12.3% to 26.0%). The increase in HDL-C level was correlated with the reduction in triglyceride levels with both IR niacin ($r$=−.33, $P$=.008) and SR niacin ($r$=−.33, $P$=.007). The HDL-C levels were significantly lower at baseline in IR niacin–treated patients, which may have influenced these results.

### Adverse Effects

Vasodilatory symptoms were reported to be at least moderately bothersome by approximately half of the patients taking IR niacin at dosages of 500 or 1000 mg/d; fewer reported these symptoms at higher dosages (Table 1). Flushing was the most frequently reported vasodilatory symptom. Patients taking SR niacin did not report an increase in vasodilatory symptoms over baseline levels. The frequency of gastrointestinal tract symptoms was increased only in patients taking 3000 mg/d of SR niacin. Fatigue was reported by patients in both the IR and SR niacin groups. Overall, global symptom scores were significantly greater than baseline for IR niacin at all dosages tested, but only at 3000 mg/d for SR niacin. The global scores for IR and SR niacin were not significantly different from each other at any dosage level.

Table 2.—Effect of Escalating Doses of Immediate- and Sustained-Release Niacin on Liver Function Tests*

| Niacin Daily Dose, mg | Mean AST, U/L | Mean ALT, U/L | Mean Alkaline Phosphatase, U/L |
|---|---|---|---|
| Immediate Release | | | |
| 0 | 22.2 | 22.7 | 95 |
| 500 | 21.3 | 21.5 | 97 |
| 1000 | 20.7 | 20.5 | 96 |
| 1500 | 21.4 | 20.7 | 98 |
| 2000 | 22.3 | 21.1 | 95 |
| 3000 | 24.3 | 22.4 | 101 |
| Sustained release | | | |
| 0 | 23.8 | 25.6 | 95 |
| 500 | 27.9 | 29.5 | 95 |
| 1000 | 40.4 | 36.3 | 106 |
| 1500 | 36.6† | 39.0† | 105 |
| 2000 | 56.5† | 59.1† | 136 |
| 3000 | 97.0† | 100.0† | 135 |

*AST indicates aspartate aminotransferase; ALT, alanine aminotransferase (usual reference interval for the study laboratory was 0 to 50 U/L for both).
†$P$<.05 vs baseline.

As dosages were escalated from 500 to 3000 mg/d, mean fasting glucose levels increased from a baseline of 5.4 mmol/L (98 mg/dL) to 5.6, 5.7, 5.9, 5.9, and 6.2 mmol/L (100, 103, 106, 106, and 112 mg/dL) with IR niacin and from 5.4 mmol/L (98 mg/dL) to 5.7, 5.6, 5.7, 6.2, and 7.5 mmol/L (102, 100, 102, 112, and 136 mg/dL) with SR niacin. Compared with baseline values, these increases were not significant with IR niacin; the increase with 2000 mg/d and above of SR niacin was significant ($P$=.009, ANOVA). By the end of the study, three patients in each group who were initially euglycemic had a fasting glucose level greater than 7.8 mmol/L (140 mg/dL). None of these patients experienced hyperglycemic symptoms, nor were they given glucose-lowering therapy. There was no appreciable change in mean uric acid levels with either the IR or SR niacin group as dosages were escalated, and no patients experienced gouty arthritis during the study. There was a substantial increase in mean liver aminotransferase and alkaline phosphatase levels in patients receiving SR niacin; these levels reached significance at 1500 mg/d and above (Table 2). There were no significant changes in liver function test results in patients receiving IR niacin.

Toxic effects severe enough to require withdrawal from therapy occurred in patients taking both dosage forms. With IR niacin, nine (39%) of the 23 patients had to be withdrawn before completing the dosage of 3000 mg/d (Table 3). The most common reasons for withdrawal from IR niacin were vasodilatory symptoms (ie, flushing, itching, rash), fatigue, and acanthosis nigricans. Withdrawals because of vasodilatory symptoms were encountered at dosages as low as 1000 mg/d, whereas acanthosis nigricans was encountered in two patients taking 2000 mg/d and one patient taking 3000 mg/d. The increase in fasting blood glucose level in patients who developed acanthosis nigricans was not different from the mean change for all patients.

The adverse effects that caused patients to withdraw from IR niacin therapy subsided completely in every case when therapy was discontinued. Recovery occurred within a few days for vasodilatory and fatigue symptoms to within several months for acanthosis nigricans. One patient who had been taking IR niacin was admitted to a local hospital 2 days after completing the study because of a bleeding peptic ulcer that required transfusion. The patient had mentioned no abdominal symptoms on his last study visit. He had a history of peptic ulcer disease but had been asymptomatic for the previous 7 years.

Eighteen (78%) of the 23 patients assigned to the SR dosage form had to be withdrawn before completing the dosage of 3000 mg/d (Table 3). Liver aminotransferase elevations more than three times the upper limit of normal were encountered in 12 of the 18 patients who were withdrawn; five of these 12 patients also had symptoms of hepatic dysfunction (ie, fatigue, nausea, anorexia). Withdrawals resulting from elevated liver aminotransferase levels

occurred at dosages as low as 1000 mg/d; symptoms of hepatic dysfunction were encountered only at the dosage levels of 2000 and 3000 mg/d. The LDL-C level in the 12 patients who withdrew because of liver function abnormalities decreased more than was expected with the dosage of niacin taken; the mean cumulative LDL-C level reduction achieved with the previous, tolerated dose was 22.7% compared with 40.5% with the "toxic" dose taken at the time of withdrawal from the study. All liver function abnormalities returned to normal within 4 weeks after niacin was discontinued.

By application of ordinal logistic regression to the period of a patient's last visit in the study before withdrawal, we did not discover a significant difference ($P$=.214) between the dosage forms for the timing of the withdrawals. However, by application of a likelihood-ratio $\chi^2$ test, we discovered a significant difference ($P$=.037) between the dosage forms for the proportion of withdrawals.

Table 3.—Patients Withdrawing From Niacin Treatment With Escalating Daily Doses and Reasons for Their Withdrawal

| | Immediate-Release Niacin | | Sustained-Release Niacin | |
|---|---|---|---|---|
| Daily Dose, mg | No. of Patient Withdrawals | Reason of Withdrawal | No. of Patient Withdrawals | Reason for Withdrawal* |
| 500 | 0 | ... | 0 | ... |
| 1000 | 4 | Nausea, flushing; itching; flushing; fatigue, rash | 2 | Fatigue; elevated LFT results |
| 1500 | 1 | Rash | 2 | Elevated LFT results |
| 2000 | 3 | Fatigue, nausea; acanthosis nigricans (2 patients) | 7 | Fatigue, listlessness; elevated LFT results; elevated LFT results and fatigue; elevated LFT results and nausea (2 patients); nausea, rash, itching; diarrhea, weight loss |
| 3000 | 1 | Acanthosis nigricans | 7 | Elevated LFT results (3 patients); elevated LFT results and anorexia; itching; nausea; elevated LFT results, nausea, vomiting, fatigue |
| Total, No. (%) | 9/23 (39) | | 18/23 (78) | |

*LFT indicates liver function test.

## COMMENT

Our study demonstrated that SR niacin reduced LDL-C levels more than IR niacin did. In concert with other controlled trials comparing IR and SR niacin, IR niacin reduced LDL-C levels 14% to 22% with dosages of 1500 to 3000 mg/d. However, SR niacin reduced LDL-C levels 22% to 50%, whereas other investigators only achieved a 13% to 25% reduction with dosages of 1500 to 3000 mg/d.[2,4] In the largest clinical study that used IR niacin, the Coronary Drug Project, 3000 mg/d reduced total cholesterol level an average of 10% in all patients receiving it and 16% in patients whose baseline total cholesterol level was greater than 7.24 mmol/L (280 mg/dL), which was similar to that achieved in patients enrolled in our study.[39]

It is not apparent why there was a difference in the LDL-C–lowering efficacy between IR and SR niacin in our study. Factors that could cause differences, including gender, race, age,[40] weight, baseline cholesterol levels, baseline triglyceride levels (which are suggestive of LDL subclass patterns[7]), and compliance, were equally distributed in the two study groups. The major difference between the groups was the prevalence of liver toxic effects associated with SR niacin, and this may have accounted for the greater LDL-C–lowering effect. Patients who experienced hepatic dysfunction with SR niacin had a greater LDL-C level reduction than was anticipated on the basis of the reduction with the previous, tolerated dose. Furthermore, nine of the 12 patients who developed hepatotoxic effects were taking the higher niacin dosages, 2000 and 3000 mg/d, suggesting a dose-related toxic effect.

Our study has also shown that IR niacin had a greater effect on increasing HDL-C levels than did SR niacin. A dosage of 1000 mg/d of IR niacin produced an impressive 25% increase in HDL-C level, whereas the greatest increase with SR niacin was only 17% with 2000 mg/d. Other controlled clinical trials have found that HDL-C level increased 14% to 37% with 1500 to 3000 mg/d of IR niacin but only 8% to 9% with similar doses of SR niacin.[2,4] Investigators using uncontrolled methods have reported increases of 25% to 41% in HDL-C level with dosages of 1000 to 3000 mg/d of SR niacin.[5,10,16]

The reason for the divergent effects of IR and SR niacin on HDL-C level is also unclear. One determinant of the efficacy in increasing HDL-C is the change in triglyceride level. A large increase in HDL-C level accompanies a large reduction in triglyceride levels[4,6,9,16] and vice versa.[6,17] This, however, does not explain the divergent effects we observed between IR and SR niacin. Both IR and SR niacin produced similar reductions in triglyceride levels, but SR niacin did not produce comparable increases in HDL-C level. This suggests that different mechanisms may be operative. It is possible that both drugs reduce the exchange of triglyceride and cholesterol ester between very-low-density lipoprotein and high-density lipoprotein particles, which results in higher HDL-C levels,[6] but that IR niacin has other effects that cause an even greater increase in HDL-C level. These mechanisms require further investigation.

One of the most important findings of our study was the extent of hepatotoxicity with SR niacin. This effect has been widely chronicled in recent years, primarily through patient case reports.[18-31] Practically all of the patients in these case reports were taking SR niacin, often after being switched from an IR to an SR dosage form.[41] None of the reports provides information on the cholesterol levels of the affected patients. In concert with our findings, most cases of hepatotoxicity have occurred in patients taking SR niacin dosages of 2000 mg/d or more. The duration of niacin therapy before hepatotoxicity is experienced has been as little as 1 week to as much as 48 months, suggesting that toxic reactions in our patients might have been even more frequent with a longer study.[41] As in our patients, symptoms accompanied some of the reported cases of elevated liver function tests; most commonly these symptoms included malaise, fatigue, somnolence, weakness, anorexia, nausea, vomiting, epigastric pain, and dark urine.[18-31] As in our patients, signs and symptoms of hepatotoxicity resolved completely within weeks of discontinuing niacin therapy. Several cases of severe liver dysfunction and fulminant hepatitis, however, have been reported, some progressing to stage 3 and 4 encephalopathy and one requiring liver transplantation.[19,24,28]

Our study is one of the few controlled trials to document a high prevalence of hepatotoxic effects with the SR compared with the IR dosage form. Hepatotoxic effects occurred in 52% of SR niacin–treated patients and 0% of IR niacin–treated patients. Christensen et al[2] and Henkin and Oberman[42] also found hepatotoxic effects in about half of their SR niacin–treated patients. Other investigators, however, have found few

cases of hepatotoxicity with SR niacin.[4,5,16,17] This suggests that there may be differences in the prevalence of this problem among the different SR niacin products. However, many different SR products with various release mechanisms, including Nicobid[20] from Rhone-Poulenc Rorer Pharmaceuticals Inc (Collegeville, Pa), Slo-Niacin[20] from Upsher-Smith (Minneapolis, Minn), Nature's Plus,[18] Niatrol,[23] Endur-Acin,[23] and generic products from Goldline[23] (used in this study), Rugby Laboratories, Rockville Center, NY,[43] and Major[20] Pharmaceutical, San Diego, have been implicated in niacin-induced hepatitis. It has also been suggested that hepatotoxic effects may be related to a contaminant introduced during the manufacture of the niacin product,[23] but there is no evidence to support this contention.

Our study results support a careful examination of the current over-the-counter availability of niacin in the United States. Only two products that have been approved by the Food and Drug Administration for use in the treatment of hypercholesterolemia are currently marketed, Niacor (Upsher-Smith) and Nicolar (Rhone-Poulenc Rorer Pharmaceuticals Inc, Collegeville). All other IR dosage forms and all SR dosage forms are available as nonprescription drugs for the treatment of nicotinic acid deficiencies and are not regulated by the Food and Drug Administration. Given the degree of toxic effects we encountered, we believe that allowing niacin to remain on the nonprescription market, where it may be used in high doses for cholesterol lowering without proper monitoring by trained health professionals, presents a potentially serious public health problem.

We also believe that the safety of niacin deserves further evaluation, especially the potential for hepatic toxic effects with SR niacin. From the perspective of a research center that routinely evaluates the efficacy and safety of drug therapies for hypercholesterolemia, the incidence and severity of adverse reactions experienced with both niacin dosage forms in the present study, but particularly with SR niacin, were much greater than any investigational drug we have evaluated for hypercholesterolemia. If niacin were being evaluated for efficacy and safety and our experiences were replicated by others, we do not believe that it would be approved by the Food and Drug Administration for use in the management of hypercholesterolemia.

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# Niacin, Used For Cholesterol, Called Toxic

## Vitamin Shouldn't Be Sold Without a Prescription, Report on Study Urges

By JERRY E. BISHOP
*Staff Reporter of* THE WALL STREET JOURNAL

A team of medical researchers said that niacin, a B vitamin that many people use to lower their cholesterol levels, is too toxic to be sold as a nonprescription drug.

The researchers found in an experiment with 46 patients that niacin taken in high enough dosages to reduce the level of cholesterol produced more adverse side effects than any experimental cholesterol-lowering drug that they tested.

The popular form of niacin that slowly releases the vitamin over several hours produced signs of liver toxicity in more than half the patients who took doses high enough to reduce their cholesterol levels, reported the team headed by James M. McKenney of the pharmacy school at the Medical College of Virginia in this week's Journal of the American Medical Association.

The older, immediate-release form of niacin produced a different, less serious group of adverse effects, including facial flush, itching, rash, fatigue and a temporary wart-like skin disfigurement in many patients.

Given the side effects, "... allowing niacin to remain on the nonprescription market, where it may be used in high doses for cholesterol lowering without proper monitoring by trained health professionals, presents a potentially serious public health problem," the team declared.

The experiments involved taking 2,000 to 3,000 milligrams of niacin a day, which involves taking from four to 12 of the 250 milligram and 500 milligram tablets sold in drug and health-food stores. Liver problems first became evident when the dosage reached 1,500 milligrams a day.

Manufacturers countered that their niacin products aren't sold to lower cholesterol levels. "We don't make niacin as an anticholesterol agent, and we don't make any claim on the package that would instruct anyone that they should take three grams a day," said Christian Boswell, marketing director for **Goldline Laboratories** in Ft. Lauderdale, Fla.

Mr. Boswell said Goldline's sustained-release form of niacin, which was used in the experiment, is a generic version of Nicobid, the brand of sustained-release niacin sold by Rhone-Poulenc Rorer Inc. of Collegeville, Pa., the U.S. unit of the big French drug maker **Rhone-Poulenc SA.**

A Rhone-Poulenc spokesman said that the company doesn't promote Nicobid sustained-release niacin for lowering cholesterol levels. It does, however, advertise its Nicolar brand of immediate-release niacin for cholesterol reduction. "We agree [with the researchers] that patients taking the immediate-release form should be monitored" by a doctor, because of the adverse effects, he said. The company's total sales of niacin are only about $1.3 million a year, he said.

Niacin has posed a dilemma for physicians and patients. Dr. McKenney and his colleagues noted, as did the Rhone-Poulenc spokesman, that the vitamin has been proven not only to lower cholesterol, but also to reduce the incidence of heart attacks and to slow the clogging of the heart's arteries. It also is the cheapest cholesterol-lowering drug around, with a 10-day supply of 500-milligram tablets costing about $2.

Widespread publicity in the late 1980s about its cholesterol-lowering effects prompted many people to begin self-medicating themselves with high dosages of niacin. Because the immediate-release form produces a high incidence of unpleasant effects, such as facial blush, many people switched to the sustained-release form that doesn't produce such effects. Doctors soon began seeing cases of liver damage in patients taking sustained-release niacin.

In the newly reported experiment, researchers gave 23 patients an immediate-release niacin, made by Rugby Laboratories of West Hempstead, N.Y., a unit of **Marion Merrell Dow** Inc., while another 23 patients took Goldline's sustained-release niacin. The dosage was increased every six weeks until it reached 3,000 milligrams a day for both groups.

At the highest dosage, the immediate-release niacin cut cholesterol levels an average of 16%, while the sustained-release form lowered cholesterol by 40%. Although the immediate-release form wasn't as effective as the sustained-release form in lowering total cholesterol levels, it was more effective in raising the HDL-cholesterol level, the so-called good form of cholesterol.

But 18 of the 23 patients taking the sustained-release form had to drop out of the experiment because blood tests indicated they were experiencing liver problems. Nine of the 23 taking the immediate-release niacin dropped out of the experiment because of side effects.

In an accompanying editorial, Louis Lasagna of Tufts University medical school in Boston, an expert in drug development, said, "Niacin still has a role to play in the management of [high cholesterol], but not on the basis of self-diagnosis and self-treatment."

## *Survey Finds One in Seven TB Cases Resists Drugs*

A WALL STREET JOURNAL *News Roundup*

One in seven cases of tuberculosis in the U.S. is resistant to drugs that previously cured the disease, the first national government survey of TB cases found.

Public-health professionals have been concerned for years about the return of tuberculosis, which was considered under control in the U.S. In the mid-1980s, strains that defy traditional drug treatment began to spread. The study, conducted by the government's Centers for Disease Control and Prevention, showed an even greater problem than thought, because the incidence of drug resistance was higher than expected, said Alan B. Bloch, a CDCP medical epidemiologist and the study's lead researcher.

Resistance arises when patients fail to complete their drug therapy, which lasts six months or longer. The hardiest TB bacteria are allowed to survive as a result, and as they multiply, they spread their genes to a new generation of bacteria—and to new victims.

The study also found that patients with some of the deadliest strains of TB—those that resist multiple drugs—may be more likely to infect other people.

Officials of the CDCP called for aggressive intervention to prevent the further spread of drug-resistant TB, including finding "every TB patient" and ensuring that patients complete their drug therapy.

The survey, published in today's Journal of the American Medical Association, collected information about TB cases reported across the country in the first three months of 1991.