Clinical Profiles of Plain Versus Sustained-Release Niacin (Niaspan) and the Physiologic Rationale for Nighttime Dosing

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Niacin is the oldest and most versatile agent in use for the treatment of dyslipidemia. It has beneficial effects on low-density lipoprotein cholesterol; high-density lipoprotein cholesterol; the apolipoproteins B and A-I constituting these fractions; triglyceride; and lipoprotein(a). Together, these benefits lead to a diminished incidence of coronary artery disease among niacin users. The chief constraints against niacin use have been flushing, gastrointestinal discomfort, and metabolic effects including hepatotoxicity. Time-release niacin has been developed in part to limit flushing, and now a nighttime formulation (Niaspan) has been developed that assists in containing this untoward effect. In a pivotal metabolic study, bedtime administration of 1.5 g time-release niacin was shown to have the same beneficial effects as 1.5 g plain niacin in 3 divided doses and to be well tolerated. Previous studies suggest that bedtime niacin administration diminishes lipolysis and release of free fatty acids to the liver; this, in turn, leads to an abolition of the usual diurnal increase in plasma triglyceride, which may result in diminished formation and secretion of triglyceride in the very-low-density lipoprotein fraction.

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In continuous use for >40 years,[1] niacin (nicotinic acid) is perhaps the most versatile agent in the clinical armamentarium against dyslipidemia in that it ameliorates every aspect of the panel of lipids, lipoproteins, and their component apolipoproteins. Niacin combines, on one hand, the potent effect of elevating high-density lipoprotein (HDL) cholesterol and diminishing triglyceride seen with fibric acid derivatives, and, on the other hand, the robust lowering of low-density lipoprotein (LDL) cholesterol encountered with the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (i.e., statins).

In addition, niacin decreases levels of a lipoprotein that is emerging as an important risk factor for coronary artery disease: lipoprotein(a). Apart from niacin, the only frequently used agent known to lower this potentially pivotal parameter is estrogen. Lipoprotein(a) shares structural homology with plasminogen and thus represents a possible connection between lipoprotein metabolism and thrombosis,[2,3] as it may interfere with plasmin generation and thus thrombolysis. In addition, lipoprotein(a) enhances trapping of LDL in the arterial wall.

The chief constraints against niacin use are 3-fold: (1) cutaneous effects (e.g., flushing, pruritus, rash, acanthosis nigricans); (2) gastrointestinal phenomena (e.g., nausea, vomiting, diarrhea, anorexia); and (3) metabolic perturbations (e.g., increases in glucose, uric acid, and hepatic enzymes). Truncal and facial flushing can be particularly troublesome to patients and lead to covert noncompliance; this, in turn, can compromise efficacy in redressing dyslipidemic derangements. This adverse effect, and dry, itchy skin, may be of particular concern to perimenopausal women and women in general.

Proper instruction and preparation can frequently help patients over the initial cutaneous discomfort and lead to prolonged adaptation and acceptable regimen adherence. Effective instruction might include giving the patient 1 niacin pill before initiating the regimen to know in advance what to expect. Taking the medication with food, use of prophylactic salicylates, and avoidance of hot beverages or soups are also potentially valuable tips. Time-release or sustained-release formulations are also of some value. In a study of 71 hypercholesterolemic patients randomly allocated to either crystalline (i.e., unmodified, plain) niacin or Nicobid (Rhône-Poulenc Rorer, Collegeville, PA), we concluded that time-release niacin "may be of particular utility for subjects who have very severe reactions to conventional niacin."[4] With the advent of Niaspan (Kos Pharmaceuticals, Miami, FL), 8–12 hours of niacin can be delivered while asleep, when patients are less likely to experience flushing.

In the same study[4] comparing plain niacin versus Nicobid, however, we also found that gastrointestinal side effects were significantly ($p < 0.05$) more common in patients randomized to time-release niacin: indigestion occurred in 12% of the time-release group compared with 0% in the plain-niacin cohort, nausea in 38% (vs 8%), vomiting in 18% (vs 0%), and diarrhea in 45% (vs 22%). Most of these symptoms represent hepatotoxicity induced when increasing the Nicobid dose from 1.5 g to 3.0 g. As a result of these untoward effects, compliance over the 6-month trial was only 64% in the time-release group compared with 90% of those assigned to unmodified drug (3 g/day).

As a result of this disparity in compliance between

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the 2 forms of niacin, lipid and lipoprotein profiles were superior in the unmodified-niacin group. LDL cholesterol was decreased by 21% in this group (vs 13% in the sustained-release group), triglyceride by 27% (vs 8%); HDL cholesterol and HDL_2 cholesterol were elevated by 26% and 38%, respectively, in the unmodified group (vs little or no change on time-release; Table I). In contrast, the efficacy of Niaspan vs plain niacin was equivalent at 1.5 g daily (Figure 1),[5] with less flushing and a comparably acceptable level of side effects.

With respect to potential untoward metabolic effects, the use of any form of niacin can adversely affect glucose disposal. For this reason, niacin may not be appropriate for certain patients with noninsulin-dependent diabetes mellitus, although the safety of Niaspan in these patients remains to be tested. The limitation of niacin use in diabetics is significant because these patients tend to have combined hyperlipidemias, a condition ideally treated with niacin. In addition, niacin of any formulation can elevate uric acid levels and is unsuitable for patients with gout unless the hyperuricemia is treated.

Finally, niacin can cause hepatotoxicity, and this is particularly the case with time-release formulations above a dosage of 2.0 g daily. In the study cited above,[4] we found that alkaline phosphatase was significantly ($p < 0.05$) elevated from months 1–4 among patients on Nicobid compared with those on crystalline niacin, and alanine aminotransferase and aspartate aminotransferase enzymes tended to be higher in the Nicobid group.

Some of the earlier time-release formulations caused hepatic necrosis,[6] and a shift from plain niacin to the time-release formulation at a high dose (2 g or higher) may also induce hepatonecrosis[7,8] and hepatotoxicity.[9] Thus, caution is advised in the use of time-release niacin above 2 g/day, and even to some extent with plain niacin.

Clinical and laboratory symptoms and signs of hepatotoxicity are important to recognize. Patients feel tired, achy, flu-like, and have "trouble getting going in the morning." These are typical symptoms of persons with any type of hepatitis. Usually the liver is not enlarged nor is it typically painful to right lower anterior rib cage percussion (Murphy's test). The laboratory signs are more specific: the aspartate aminotransferase level (which we prefer to follow) almost always increases, but often surprisingly little for the amount of fatigue and malaise present. The increase in either aspartate aminotransferase or alanine aminotransferase may be only 2-fold and only marginally above the upper limit of normal. However, combined with the characteristic lipoprotein lipid changes, the diagnosis of lipid-lowering drug-induced toxicity becomes clearer. Typically, in cases of hepatic toxicity the LDL-cholesterol reduction is "too good to be true" (that is, greater than expected); the HDL-cholesterol level also decreases, rather than increasing, as one would expect with niacin treatment. Table II describes a review of a series of cases taken from our clinic files demonstrating these relations. None of these cases was associated with Niaspan use. In fact, clinical experience indicates that the hepatotoxicity of Niaspan is comparable to that of plain niacin.[5]

TABLE I Lipoprotein and Apolipoprotein Levels: Plain Niacin Versus Nicobid (Time-Release)

	Plain Niacin (mg/dL)		Nicobid (mg/dL)	
	Baseline	6 mo	Baseline	6 mo
TG	174	119	169	159
TC	290	249	277	257
LDL-C	209	168	203	179
HDL-C	49	64	47	55
HDL_2-C	14.5	19.8	14.5	13.8
HDL_3-C	31.1	40.0	27.4	37.0
Apo A-I	122	137	118	130

Apo A-I = apolipoprotein A-I; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglyceride.

Reproduced with permission from *Metabolism*.[4]

TABLE II Characteristics of Niacin Toxicity from Twelve Clinical Cases

Dose (g)	Symptoms	AST (mg/dL)	Total Cholesterol (mg/dL)	
			Baseline	Toxic
1.5 TR	Diarrhea, weakness	122	322	186
3.0 TR	Lethargy	50	228	—
2.5 TR	Nausea	146	222	188
3.0 TR	Nausea	47	218	181
1.5 TR	Anorexia	73	271	125
4.0 TR	Fatigue, GI	96	302	167
3.0 TR	Lethargy, GI	228	215	—
1.5	Fatigue	47	277	268
6.0	Anorexia, GI	93	319	293
3.0	Unwell	81	280	193
2.5	Tired	304	256	171
3.0	Nausea, sick	182	249	108

AST = aspartate aminotransferase; GI = gastrointestinal; TR = time release.

PHYSIOLOGIC RATIONALE FOR NIGHTTIME DOSING

Approximately 25 years ago, Schlierf and Dorow[10] published an intriguing article that continues to find scientific interest today. In a metabolic study of 10 patients with type IV hyperlipoproteinemia and 10 normals, these investigators observed a diurnal variation in plasma triglyceride levels, such that triglyceride tended to be higher at night than during the morning and afternoon hours.

During the nocturnal fast, the body turns toward adipose tissue fatty acids as a source of metabolic fuel. Lipolysis leads to release of free fatty acids for use as energy by tissues (Figure 2). Niacin tends to diminish lipolysis, possibly by acting on hormone-sensitive lipase. As a result, a smaller quantity of free fatty acids is transported to the liver during niacin therapy. The liver, in turn, esterifies fewer of these free fatty acids as triglyceride in very-low-density lipoprotein (VLDL). It is likely that a decreased formation of

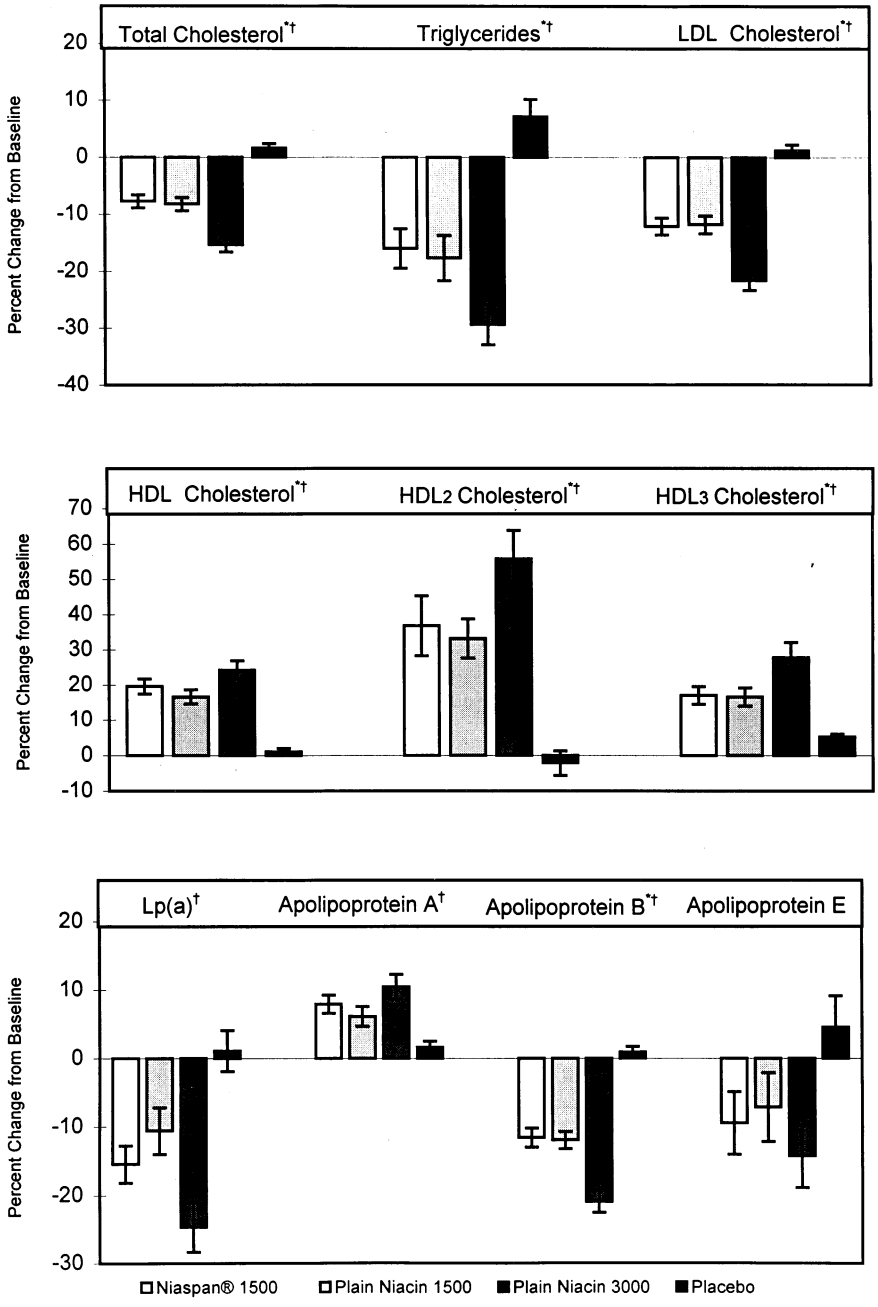

FIGURE 1. Percent changes from baseline of lipids, lipoproteins, and apolipoproteins. All differences between active treatment and placebo are statistically significant, except for apolipoprotein E between plain niacin 1,500 mg and placebo (p = 0.085). Niaspan and placebo data are the means of weeks 8, 12, and 16 values. Plain niacin data at 1.5 g daily are from week 8 and at 3.0 g daily are the means of weeks 12 and 16. *Significant at the 0.05 level between Niaspan and plain niacin 3,000 mg. †Significant at the 0.05 level between plain niacin 1,500 mg and plain niacin 3,000 mg. LDL = low-density lipoprotein; HDL = high-density lipoprotein; Lp(a) = lipoprotein(a). (Reproduced with permission from *Metabolism.*[5])

VLDL can lead to a decreased generation of LDL cholesterol, although niacin could exert a direct effect on LDL-cholesterol generation as well.

In addition, niacin is thought to help enhance reverse cholesterol transport. Reverse cholesterol transport is believed to result from increases in concentrations of HDL_3 and HDL_2, which are then taken up by the liver or recycled back to LDL.

Schlierf and Dorow[10] found that niacin abolished the nocturnal increase in plasma triglyceride levels, whereas control subjects who received no niacin exhibited an approximate doubling in triglyceride con-

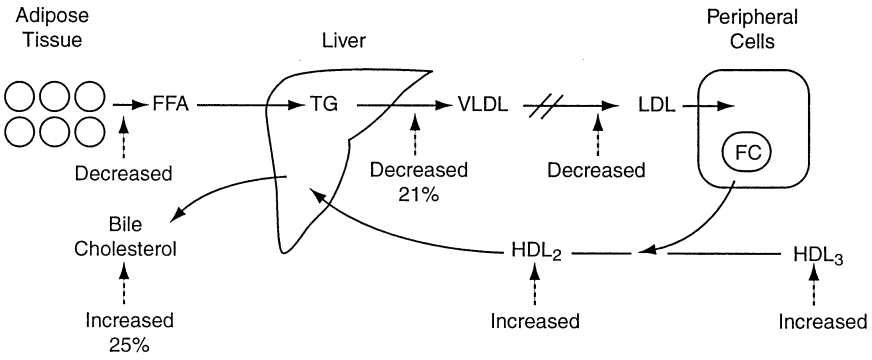

FIGURE 2. The proposed mechanisms of the effects of niacin on lipoprotein metabolism. FC = free cholesterol; FFA = free fatty acid; HDL = high-density lipoprotein; LDL = low-density lipoprotein; TG = triglyceride; VLDL = very-low-density lipoprotein. (Reproduced with permission from *Metabolism*.[4])

centration overnight. Figure 3 shows a 24-hour plot of free fatty acids and triglyceride. Between hours 18 and 8, a dose of 2 g of niacin (nicotinic acid) decreased the levels of both of these components.

It should be noted that cholesterol biosynthesis also peaks in the evening. HMG-CoA reductase inhibitors act by diminishing this activity, which, in turn, leads to upregulation of LDL receptors (apolipoprotein B, apolipoprotein E) and enhanced clearance. HMG-CoA reductase inhibitors are, therefore, also frequently administered at night, either with the evening meal or at bedtime.

Thus, combined administration of a statin with niacin would be highly convenient and might promote

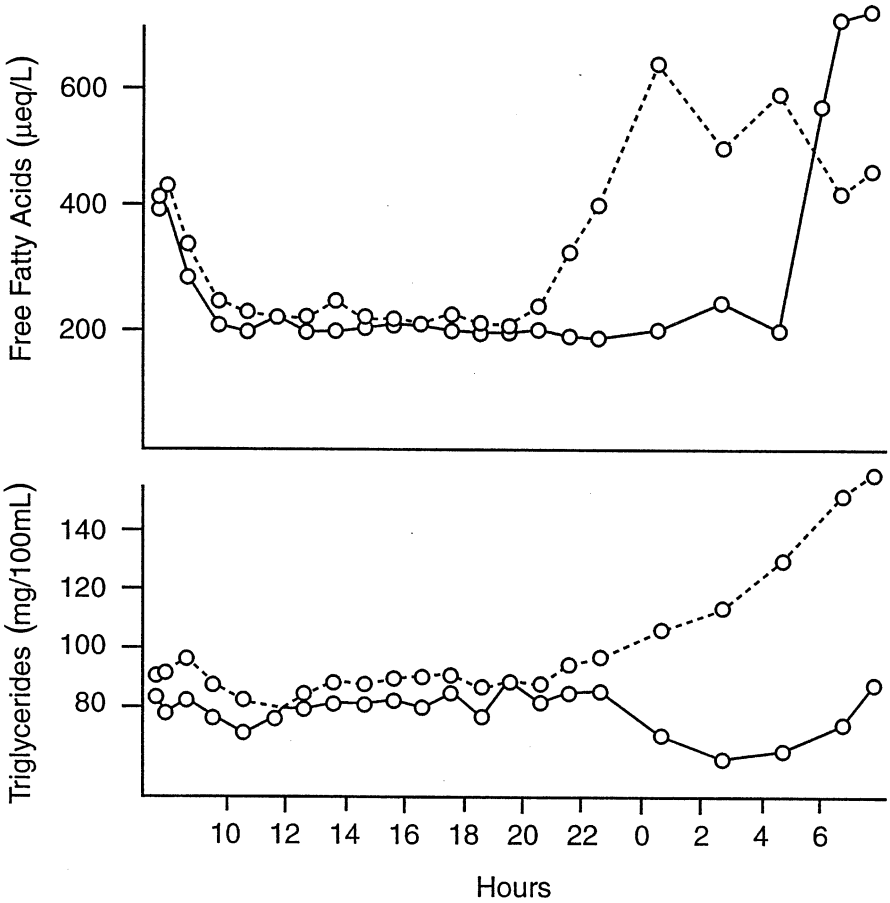

FIGURE 3. Mean 24-hour plasma free fatty acid and triglyceride levels. Nocturnal administration of niacin abolishes the diurnal increase in these parameters (without nocturnal infusion, dotted lines; with nocturnal infusion, solid lines). (Reproduced with permission from *J Clin Invest*.[10])

compliance. Niacin, together with HMG-CoA reductase inhibitors, constitutes a safe and effective therapeutic combination that leads to impressive changes in the entire lipid and lipoprotein panel.[11,12] Niaspan has also been tested with a statin in a recent randomized study, and the efficacy and safety of this combination were as good as with plain niacin and a statin.[13]

CONCLUSION

Niacin is a nearly ideal drug for the management of the combined hyperlipidemias. A newer time-release formulation of niacin given as a single 1.5-g dose at bedtime has an effect equivalent to plain niacin. Unlike some other time-release formulations, it appears to be no more hepatotoxic than plain niacin.

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