Does extended release nicotinic acid reduce the risk of hepatotoxicity compared to immediate release nicotinic acid?

Nicotinic acid (synthetic niacin or 3-pyridinecarboxylic acid) is a water soluble B-complex vitamin (i.e., vitamin B_3).[1] The terms nicotinic acid and niacin are used interchangeably in the literature and in this response. Initially approved by the Food and Drug Administration (FDA) in 1938 for the prevention and treatment of pellagra (a disease caused by niacin deficiency), nicotinic acid was subsequently FDA-approved for use as an antilipemic agent at much higher doses.[2] Niacin (in its unmodified immediate release [IR] crystalline form) was the first drug that demonstrated the ability to prevent myocardial infarction (MI)[3] as well as all-cause mortality[4] by lowering cholesterol. As a result, nicotinic acid was recommended as a first-line pharmacologic treatment option along with bile acid sequestrants for reducing low-density lipoprotein cholesterol (LDL-C) in National Cholesterol Education Program (NCEP) guidelines from 1988 until 2002.[5,6] The 2002 NCEP Adult Treatment Panel III guidelines listed nicotinic acid along with bile acid sequestrants as alternatives to 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (HMG-CoA reductase inhibitors, i.e., statins) when initiating drug therapy to reduce LDL-C.[7] Table 1 lists the formulations of nicotinic acid currently marketed in the United States.

Table 1: Currently available formulations of nicotinic acid available in the US [2,8-11]

Formulation & Strength(s)	**Trade Name**	**FDA-Approved Indication(s)**	**Usual Daily Dose**
Immediate release nicotinic acid, 500 mg crystalline tablet	Niacor® (OTC products sold as nutritional supplements also available)	*"Alone or in combination with a bile-acid binding resin, as an adjunct to diet for the reduction of elevated total and LDL cholesterol levels in patients with primary hypercholesterolemia (Types IIa and IIb), when the response to a diet restricted in saturated fat and cholesterol and other nonpharmacologic measures alone has been inadequate."* [8]	1.5 – 3 g Divided 3 times daily
Extended release nicotinic acid, 500 mg, 750 mg, and 1000 mg film-coated tablets	Niaspan® (Generic products also available as film-coated and non-film-coated tablets)	*"To reduce elevated TC, LDL-C, Apo B and TG, and to increase HDL-C in patients with primary hyperlipidemia and mixed dyslipidemia.* *"To reduce the risk of recurrent nonfatal myocardial infarction in patients with a history of myocardial infarction and hyperlipidemia.* *"In combination with a bile acid binding resin:* - *Slows progression or promotes regression of atherosclerotic disease in patients with a history of coronary artery disease (CAD) and hyperlipidemia.* - *As an adjunct to diet to reduce elevated TC and LDL-C in adult patients with primary hyperlipidemia. "To reduce TG in adult patients with severe hypertriglyceridemia."* [9]	1 – 2 g At bedtime
Sustained release nicotinic acid, 250 mg, 500 mg, and 750 mg tablets	Slo-Niacin® (and other OTC products)	Not FDA-approved for any uses Available only as an OTC nutritional supplement[10,11]	1 – 2 g Morning or evening

Apo B=apolipoprotein B; FDA=Food and Drug Administration; HDL-C=high-density lipoprotein cholesterol; OTC=over-the-counter; TG=triglycerides; US=United States

Immediate vs. Sustained Release Nicotinic Acid

The IR formulation of nicotinic acid, dosed multiple times a day, is most commonly associated with mild to severe cutaneous flushing, warranting slow titration to the maximum dose and pretreatment with aspirin or another non-steroidal anti-inflammatory drug.[8] Sustained release (SR) formulations of nicotinic acid have been available over-the-counter for many years and were developed in an effort to minimize these side effects and improve adherence to treatment, but they have been associated with increased risk of hepatotoxicity.[12] A 1992 FDA review of hepatotoxicity associated with IR and SR niacin formulations identified 6 case reports of hepatotoxicity with IR niacin (all at high doses, ≥3 g/day), 2 cases associated with SR niacin and 10 cases of hepatotoxicity occurring after patients intentionally or unintentionally switched from IR niacin to SR niacin.[13] Three of the cases involving SR niacin resulted in fulminant hepatic failure. A more recent case report, published in 2012, described a 69-year-old male who developed hepatotoxicity upon switching to SR niacin at the same dose (3 g/day) of IR niacin he had been taking for the previous 5 years; symptoms and elevated liver enzymes resolved upon discontinuation of SR niacin and remained normal when the patient was restarted on IR niacin at 3 g/day.[14] While the SR formulations are not regulated by the FDA, a randomized controlled trial (RCT) published in 1994 compared the safety and effectiveness of IR vs. SR formulations of niacin; 78% of patients receiving SR niacin compared to 39% of patients receiving IR niacin withdrew from the study, with 52% vs. 0%, respectively, experiencing elevated liver enzymes and/or symptoms of hepatotoxicity, leading investigators to conclude that use of the SR formulation should be restricted.[15] An extended release (ER) formulation of nicotinic acid was subsequently developed with an intermediate dissolution rate in an effort to mitigate flushing as well as hepatotoxic effects; it was approved by the FDA in 1997.[9]

The mechanism by which flushing and hepatotoxicity are associated with different formulations of niacin can be explained by the dual metabolic pathway of the drug.[12,16] Nicotinic acid undergoes saturable first-pass metabolism via both a conjugative and a non-conjugative (amidation) pathway. The conjugative pathway produces prostaglandins that cause vasodilation and flushing. The amidation pathway produces nicotinamide and pyrimidine metabolites that are associated with hepatotoxicity. The amidation pathway is a high-affinity, low capacity pathway and the conjugation pathway is a low-affinity, high capacity pathway. Therefore, the rapid dissolution of IR niacin quickly saturates the amidation pathway, leaving more of the drug to be conjugated, causing more flushing. The slower dissolution of the SR formulations results in even more of the drug passing through the amidation pathway, yielding more of the hepatotoxic metabolites. The intermediate dissolution rate of ER niacin results in a more balanced metabolic and side effect profile compared to IR and SR niacin.[17]

Immediate vs. Extended Release Nicotinic Acid

A search of the literature identified 2 head-to-head RCTs that compared IR and ER formulations of nicotinic acid.[18,19] One of these studies focused on efficacy in the treatment of various LDL-C subclasses and did not report any findings related to safety.[18] The other study, by Knopp et al, was a multicenter double-blind randomized placebo-controlled trial that compared the safety and efficacy of the currently available ER niacin to IR niacin in the treatment of patients with hyperlipidemia.[19] Patients were included if they had been stabilized on the NCEP Step One diet and had LDL-C ≥190 mg/dL or ≥160 mg/dL with history of coronary heart disease (CHD) or at least 2 CHD risk factors. Exclusion criteria included high-density lipoprotein cholesterol (HDL-C) ≥70 mg/dL, uncontrolled or insulin-dependent

diabetes and liver function markers ≥1.3 times the upper limit of normal (ULN). Patients were randomized to receive IR niacin, ER niacin, or placebo with all patients instructed to take identical looking tablets 4 times daily (once after each meal and at bedtime). Doses of ER and IR formulations were titrated to 1.5 g daily by week 4; ER niacin was continued at a maximum dose of 1.5 g (at bedtime) through week 16; IR niacin was continued at 1.5 g daily through week 8, then titrated to a maximum dose of 3 g (1 g thrice daily with meals) in week 9 and continued through week 16. The primary endpoint was change from baseline in LDL-C at weeks 8, 12 and 16.

A total of 223 patients were randomized to receive ER niacin (n=76), IR niacin (n=74) or placebo (n=73).[19] Baseline characteristics were similar with the exception of significantly more smokers in the IR group compared to the ER group (15% vs. 4%, p<0.05). Medication adherence as measured by pill counts was >90% in all groups. Overall mean reductions in LDL-C from baseline were 12%, 12% and 22% for ER niacin, low dose (1.5 g/day) IR niacin, and high dose (3 g/day) IR niacin, respectively (p<0.05 for all comparisons vs. placebo as well as high dose IR vs. ER and low dose IR). Mean increases in hepatic aspartate aminotransferase (AST) compared to baseline for ER niacin were significant (p<0.05) at 8 weeks (10.7%) but not at 12 weeks (4.0%) or 16 weeks (4.4%); mean AST increase with low dose IR niacin was not significant at 8 weeks (5.2%) but AST increases with high dose IR niacin were significant at weeks 12 and 16 (14.7% and 10.8%, respectively.) Two patients in the ER niacin group and 1 patient in the low dose IR niacin group experienced increased AST >2 times ULN. There were no significant increases in hepatic alanine amino transferase (ALT) in any group and no patients who experienced ALT elevations >2 times ULN. One patient in the ER niacin group and 1 patient receiving IR niacin withdrew due to liver enzyme elevations >2 times and >3 times ULN, respectively, whereas 3 patients receiving ER and 3 receiving IR withdrew due to flushing. The authors concluded that 1.5 g ER niacin dosed at bedtime had a similar effect on hepatic enzymes compared to the 1.5 g IR niacin dose divided 3 times daily.

Product labeling for both prescription formulations of nicotinic acid (IR and ER) contain the same warning that severe hepatic toxicity, including fulminant liver failure, has occurred in patients substituting SR niacin for IR niacin at equivalent doses.[8,9] The manufacturer of ER niacin specifically states that the ER preparation should not be substituted for equivalent doses of IR niacin and if a patient is switched from IR to ER niacin, the ER dose should be initiated at 500 mg at bedtime and titrated to therapeutic effect.[9] Both package inserts also recommend monitoring liver enzymes before and during treatment.[8,9]

Current Evidence-Based Guidance

The most recent dyslipidemia guidelines/position statements from the American Association of Clinical Endocrinologists and American College of Endocrinology (2017),[20] the National Lipid Association (2015)[21] and the International Atherosclerosis Society (2013)[22] recommend niacin primarily as adjunct therapy for reducing triglycerides since adding niacin to aggressive statin therapy for secondary prevention failed to show additional benefit for reducing all-cause mortality, CHD mortality, MI or stroke in 2 large RCTs.[23,24] Of note, this caveat is also stated in the ER niacin product label as a limitation of use.[9]

A Cochrane systematic review of niacin for primary and secondary prevention of cardiovascular events was published in 2017 and was based on evidence that was current through August of 2016.[25] The

review included 23 RCTs comparing niacin to placebo in a total of 39,195 participants. Niacin failed to reduce the risk of all-cause, cardiovascular or non-cardiovascular mortality, as well as fatal or non-fatal MI or stroke, and participants randomized to receive niacin were more likely to discontinue treatment due to side effects (relative risk [RR] 2.17, 95% confidence interval [CI] 1.70 to 2.77; participants=33,539; studies=17; I^2 = 77%; moderate-quality evidence for the subset of safety data). The authors concluded, based on overall moderate- to high-quality evidence, that niacin has no role in the primary or secondary prevention of cardiovascular events, either as monotherapy or add-on therapy, and that continued research in RCTs would be unethical.

Conclusion

Nicotinic acid has been used at pharmacologic doses in both IR and SR formulations to treat hyperlipidemia for several decades. The dual metabolic pathway of niacin yields differential side effects based on dissolution rates of the formulations, particularly at higher doses. Cutaneous flushing is more commonly associated with IR niacin, whereas hepatotoxicity has been more frequently reported with SR niacin, in particular when switching from IR to SR formulations at the same dose. ER nicotinic acid was developed with an intermediate dissolution rate in an effort to mitigate these adverse effects, however comparative safety data are limited. Results of 1 head-to-head RCT comparing IR and ER formulations of niacin for up to 16 weeks demonstrated that at equivalent doses (1.5 g/day) elevations in hepatic enzymes were transient or insignificant.[19] As warned in the product labeling, patients should not be switched from IR niacin to ER niacin at equivalent dosing, but should be started at the lowest dose of the ER formulation (500 mg) and titrated to therapeutic effect. Liver enzymes should be monitored before and during therapy with either formulation. Lastly, when weighing the risks vs. benefits of niacin for treatment of dyslipidemia, consideration should be given to the more recent clinical guidelines, which limit niacin's role to adjunct treatment of hypertriglyceridemia, and the Cochrane systematic review, which recommends no role at all for niacin in the primary or secondary prevention of cardiac events.

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