Overview of niacin formulations: Differences in pharmacokinetics, efficacy, and safety

JOHN A. PIEPER

Abstract: The pharmacokinetics, efficacy, and safety of niacin and its various formulations are discussed.

Niacin has been used for decades for the treatment of dyslipidemia because of its favorable effects on all lipoprotein parameters. Niacin significantly increases high-density lipoprotein cholesterol (HDL-C) more than any other available agent and reduces total cholesterol, low-density lipoprotein cholesterol (LDL-C), lipoprotein (a), and triglycerides. Niacin is currently available in immediate-release (IR), sustained-release (SR), and extended-release (ER) formulations that differ in their dissolution, pharmacokinetic, efficacy, and safety profiles. Important drawbacks to niacin therapy such as cutaneous flushing, associated with IR niacin, and hepatotoxicity, associated with SR niacin, have historically limited its use. The adverse effect profiles of the different niacin formulations can be explained by differences in their dissolution and absorption rates and metabolic disposition, which result in production of metabolites associated with the respective adverse effects. The ER niacin formulation, with an intermediate dissolution rate between the dissolution rates of IR and SR niacin, demonstrates reduced rates of cutaneous flushing compared with IR niacin and hepatotoxic effects compared with SR niacin. Pharmacists need to be familiar with the pharmacokinetics, efficacy, and safety of available niacin formulations so that they can optimally educate both patients and health care providers on the differences among niacin formulations, counsel on the proper selection of a niacin product, and provide strategies for improving tolerance and adherence to therapy.

Index terms: Absorption; Antilipemic agents; Compliance; Dissolution rates; Formulations; Hyperlipidemia; Metabolism; Niacin; Patient information; Patients; Pharmacokinetics; Release; Sustained action medications; Toxicity

Am J Health-Syst Pharm. 2003; 60(Suppl 2):S9-14

Niacin, also known as nicotinic acid, was first introduced in the mid-1950s as an immediate-release (IR) formulation.[1] Niacin significantly increases high-density lipoprotein cholesterol (HDL-C) more than any other available agent while reducing total cholesterol, low-density lipoprotein cholesterol (LDL-C), lipoprotein (a), and triglycerides.[2-4] Niacin has several proposed mechanisms by which it alters lipid metabolism. Niacin increases HDL-C levels by blocking hepatic uptake of apolipoprotein A-1 and decreasing HDL clearance.[3,5] By inhibiting the mobilization of free fatty acid from peripheral tissues, niacin reduces hepatic triglyceride synthesis and secretion of very-low-density lipoprotein cholesterol (VLDL-C) and may also inhibit the conversion of VLDL into LDL.[2,6,7] It has been shown that niacin therapy and the accompanying improvements in the lipid profile significantly reduce total mortality and coronary events in patients with a history of documented coronary heart disease.[8,9]

The three formulations of niacin that are currently available differ with respect to dissolution rates, which in turn influence their metabolic fate. IR niacin is currently approved by FDA for the treatment of dyslipidemia and is available by prescription (Niacor, Upsher-Smith Laboratories) as well as several over-the-counter agents. Although it is highly effective, its use is associated with a relatively high incidence of adverse effects, mainly prostaglandin-mediated cutaneous facial and truncal flushing characterized by warmth, redness, and itching. The IR formulation needs to be administered two or three times a day, which creates adherence problems. In the mid-1960s sustained-release (SR) niacin was developed with the aim of reducing the incidence of flushing. Although SR niacin modifies lipid parameters while causing fewer cutaneous adverse effects than IR niacin, mounting clinical experience suggests that some

JOHN A. PIEPER, PHARM.D., FCCP, BCPS, is Dean and Professor, College of Pharmacy, University of New Mexico, 2502 Marble NE, Albuquerque, NM 87131-5691 (jpieper@salud.unm.edu).

Based on the proceedings of a symposium held December 9, 2002, during the ASHP Midyear Clinical Meeting in Atlanta, GA, and supported by an unrestricted educational grant from Kos Pharmaceuticals, Inc. Dr. Pieper received an honorarium for participating in the symposium.

of these formulations are associated with an increased incidence of other adverse effects including gastrointestinal intolerance and hepatotoxicity.[10-13] SR niacin is not FDA approved for the treatment of dyslipidemia and is available over the counter as a dietary supplement. Extended-release (ER) niacin, with a dissolution rate intermediate between IR and SR niacin formulations, has been FDA approved for the management of dyslipidemia and is available by prescription (Niaspan, Kos Pharmaceuticals). ER niacin has demonstrated lipid-altering efficacy comparable to IR and SR niacin but appears to have improved tolerability and safety characteristics.[14]

Niacin metabolism

The flushing and hepatotoxicity associated with IR and SR niacin, respectively, are directly related to the dissolution rates of the formulations and the metabolic characteristics of niacin.[13] Niacin undergoes extensive first-pass metabolism in the liver, where it is processed by two pathways, the conjugative pathway and the amidation pathway (Figure 1).[3] The conjugative pathway results in the formation of glycine conjugates of niacin, such as nicotinuric acid (NUA), which have been associated with vasodilation and flushing.[3,15] This is a low-affinity, high-capacity pathway that is only utilized when the amidation pathway has been saturated.[3]

The amidation pathway results in the formation of nicotinamide and pyrimidine metabolites, which have been associated with the hepatotoxicity seen with some SR niacin formulations. The amidation pathway is high affinity and low capacity. When this pathway is saturated, niacin can only be metabolized by the conjugative pathway.

Because of its rapid dissolution and absorption, IR niacin saturates the amidation pathway causing most of the drug to be metabolized by the conjugative pathway, which results in a high rate of flushing. SR niacin releases the drug more slowly over time causing the majority of drug to be metabolized by the amidation pathway, thus generating a relatively greater amount of metabolites associated with hepatotoxicity.[3]

A simulation model describing the metabolism of niacin after administration of equal doses (1000 mg) of the three available formulations can be used to illustrate how the dissolution rate controls the metabolic profile (Figure 2). The model assumes that the amidation pathway is saturated when niacin is released at 40 mg/hr or greater.

IR niacin is absorbed at a rate of approximately 500 mg/hr. Therefore, two hours after administration of 1000 mg IR niacin, the full dose (100%) will have been released. Assuming an absorption rate of 50 mg/hr for SR niacin, only 100 mg (10%) of a 1000-mg dose of SR niacin would be released in the same time. The amidation pathway will be quickly saturated in patients receiving IR niacin with only 80 mg of the IR niacin dose metabolized by the amidation pathway, resulting in few amidation metabolites. By contrast, 920 mg will be metabolized by the conjugative pathway. After 24 hours, 1000 mg (100%) of the SR niacin dose will have dissolved, 800 mg will have been metabolized via the amidation pathway, and 200 mg will

Figure 1. Pathways for niacin metabolism. Reprinted with permission. NUA = nicotinuric acid, NAM = nicotinamide, 6HN = 6-hydroxynicotinamide, MNA = *N*-methylnicotinamide, NNO = nicotinamide-*N*-oxide, NAD = nicotinamide adenine dinucleotide, 2PY and 4PY = pyridone metabolites.

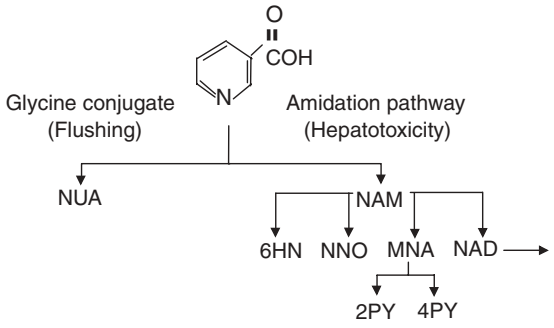
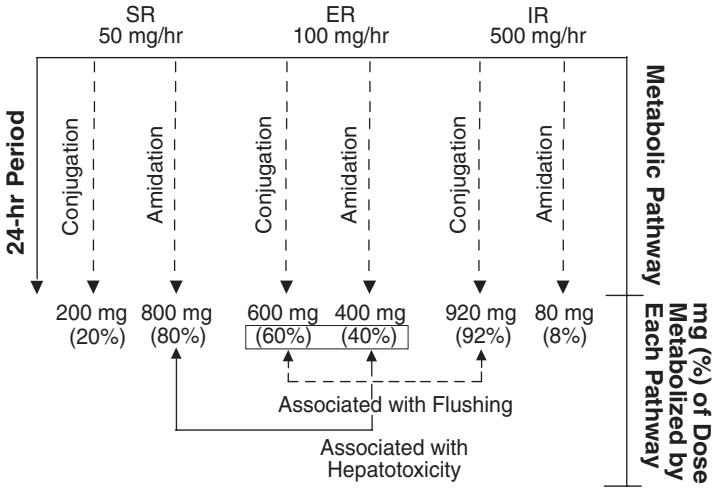


Figure 2. Simulation of niacin metabolism using a 1000-mg dose. SR = sustained release, ER = extended release, IR = immediate release.



have been metabolized via the conjugative pathway.

The ER formulation has a dissolution rate of approximately 100 mg/hr. A 1000-mg dose of ER niacin would be completely absorbed after 10 hours and would be expected to generate 400 mg of amidation metabolites and 600 mg of NUA with the simulation model. With the lower proportion of ER niacin metabolized to amidation products as compared with SR niacin (40% versus 80%), ER niacin would be expected to have a lower hepatotoxic risk compared to the SR niacin formulations. ER niacin would also be expected to produce a lower proportion of glycine conjugates than IR niacin (60% versus 92%) and, therefore, a lower incidence of flushing.

The general predictions of this model are supported by results from a small, randomized, crossover trial comparing the pharmacokinetics of IR and SR niacin in 10 healthy volunteers.[16] Patients were given a single 500-mg dose of IR niacin, subsequently underwent a one-week washout period, and were then administered 500 mg of SR niacin. The urinary excretion (milligrams per day) of NUA and 2-pyridone, a product of the amidation pathway, was measured after each administered dose. IR niacin administration resulted in more NUA (78 ± 14 mg of NUA) than SR niacin (19 ± 4 mg), a four-to-one ratio, which is similar to that predicted by the simulation.[16]

Clinical trial comparisons of niacin formulations

The pharmacokinetic characteristics of niacin and the dissolution rates of the various niacin products dictate the metabolic products and the differential adverse effect profiles of the formulations. Clinical studies have been conducted that clearly demonstrate these differences.

IR versus SR niacin. A number of small clinical studies have compared the efficacy, safety, and tolerability of IR and SR niacin formulations, revealing important differences in terms of lipid modification and adverse effect profiles. In a 1985 study, 71 hyperlipidemic patients were randomly assigned to receive IR or SR niacin for six months.[11] All patients received 1500 mg/day of IR or SR niacin for one month, after which the dose was titrated to 3000 mg/day. Lipid values, blood chemistry, liver enzymes, symptomatic adverse effects, and compliance with therapy were assessed. SR niacin was associated with slightly greater decreases in total cholesterol than IR niacin at one month, but the mean two- to six-month decrease was similar for both formulations for total cholesterol, 15.1% reduction with IR versus 11.5% reduction with SR, and LDL-C, 21% reduction with IR and 13% reduction with SR (Figure 3, A and B). Although no significant difference in triglyceride reduction was seen between agents, there was a clear trend toward a more consistent reduction with IR niacin (Figure 3, C). IR niacin led to significant increases in mean HDL-C values (a two- to six-month mean increase of 26% for IR and 9% for SR, $p < 0.05$) (Figure 3, D). In terms of safety, SR niacin was associated with significant increases in alkaline phosphatase (AP) levels and nonsignificant increases in alanine aminotransferase (ALT) levels; there was no change in AP or ALT levels in patients receiving IR niacin. Flushing occurred in statistically similar proportions of patients receiving IR and SR niacin (100% and 82%, respectively). Other adverse effects including indigestion, nausea, diarrhea, sexual dysfunction, and fatigue were significantly more frequently observed with SR niacin. On average, patients assigned to SR niacin were able to tolerate a mean dose of 2000 mg/day compared to a mean dose of 2700 mg/day in the IR niacin group. Similar proportions of patients in both IR and SR niacin treatment groups (25% and 18%, respectively) discontinued the study because of adverse events (flushing, pruritus, and mucous membrane irritation with IR niacin; flushing, nausea, and fatigue with SR niacin).[11]

In a 1994 study, 46 patients were

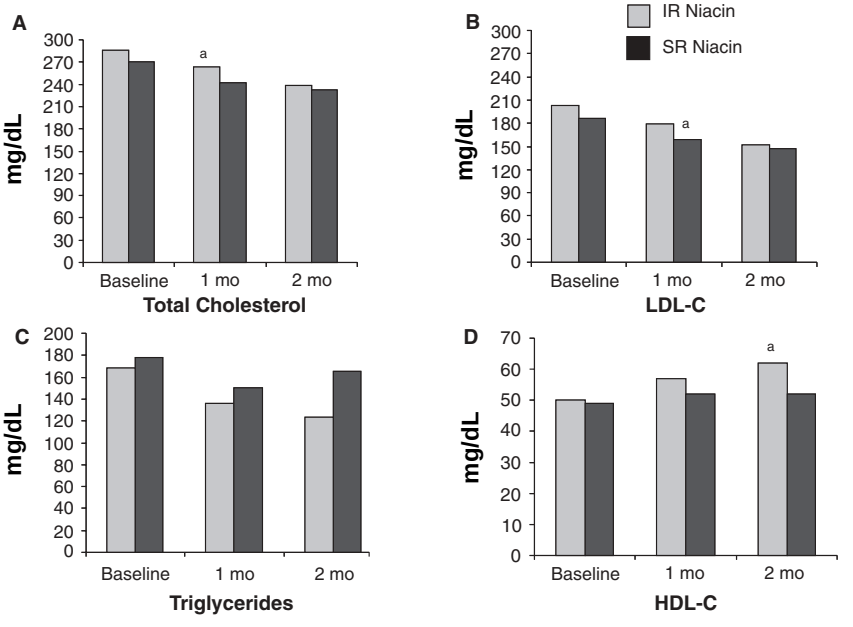


Figure 3. Effects of IR niacin and SR niacin on lipids and lipoproteins in 71 dyslipidemia patients.[11] HDL-C = high-density lipoprotein cholesterol, IR = immediate release, LDL-C = low-density lipoprotein cholesterol, SR = sustained release. [a]$p < 0.05$.

randomly assigned to receive IR or SR niacin for a period of 30 weeks.[10] Doses of each were escalated every six weeks, after an initial six-week run-in period, beginning with 250 mg/day for one week, which was increased to 500 mg/day for the next five weeks. Doses of each formulation were increased to 1000, 1500, 2000, and finally 3000 mg/day for six weeks each. Lipid profiles, blood chemistries, symptomatic adverse effects, adherence to therapy, and liver enzymes were assessed at the end of each study period. Both IR and SR niacin formulations produced dose-dependent reductions in LDL-C; SR niacin was significantly more effective than IR niacin in reducing LDL-C levels at doses of ≥1500 mg/day. Dose-related reductions in triglycerides were also seen for both products. At the 1000-mg/day dose, IR niacin produced a 29% reduction in triglycerides compared with 7% with SR niacin ($p = 0.009$). At daily doses of ≥1500 mg, reductions in triglyceride levels were not significantly different between IR and SR niacin. IR niacin led to significantly greater increases in HDL-C than SR niacin at all doses. By the end of the study, 3000 mg of IR and SR niacin resulted in a 22% and 50% reduction in LDL-C, a 42% and 41% reduction in triglycerides, and a 35% and 9% increase in HDL-C, respectively.[10]

Levels of ALT and aspartate aminotransferase (AST) were not significantly increased in patients receiving IR niacin at any dose. In contrast, both enzymes increased approximately four times above baseline in patients receiving SR niacin; increases were significant at 1500 mg/day and higher.[10] As expected, flushing was more common in patients treated with IR niacin, occurring in up to 53% of patients compared with 22% in the SR niacin group. However, decreases in the incidence of flushing with IR niacin were observed even as the dose was titrated up; by study end only 29% of patients continued to report flushing episodes. Gastrointestinal disturbances occurred in up to 56% of patients receiving SR niacin compared with 39% of patients treated with IR niacin. A significantly larger proportion of patients in the SR niacin group (78%) were withdrawn due to adverse events than in the IR niacin group (39%; $p < 0.04$). The most common reasons for withdrawal were flushing, itching, and rash in the IR niacin group and elevated aminotransferase levels in the SR niacin group. Specifically, 12 of the 18 SR niacin-treated patients who withdrew had liver enzyme levels more than three times the upper limit of normal without achieving the target dose of 3000 mg/day and 5 of the 12 patients had symptoms of hepatic dysfunction.[10]

IR versus ER niacin. The efficacy and safety of ER niacin have also been compared with IR niacin. Results of a double-blind trial of 223 dyslipidemic patients who were randomly assigned to receive IR niacin, ER niacin, or placebo for 16 weeks have been published.[14] During weeks 1 through 4, all patients had niacin doses titrated gradually. IR niacin was taken in three equally divided doses; the dose was titrated up to 3000 mg/day after 8 weeks and remained constant during weeks 9 through 16. ER niacin was taken once daily at bedtime; the dose was held constant at 1500 mg/day for weeks 5 through 16 of the study. The lipid-modifying effects of 1500 mg/day for IR and ER niacin were found to be similar. Triglyceride levels were decreased 16% and 18% from baseline in the ER and IR (1500 mg/day) group, respectively. Similar reductions in total cholesterol and LDL-C levels were also seen (8% and 12%, respectively, for both), as were increases in HDL-C (20% and 17%, respectively). An approximate doubling of these effects was seen with IR niacin 3000 mg/day, which was significantly greater than the effects seen with IR or ER formulations at 1500 mg/day.[14]

ER and IR niacin had similar effects on both ALT and AST levels (Figure 4).[14] With 1500 mg/day, neither formulation was found to consistently increase mean levels of AST and ALT above baseline values. At the 3000-mg/day dose of IR niacin, significant elevations in AST, but not ALT, levels were observed. During weeks 1 and 2, significantly more patients flushed with IR niacin (54 patients) versus ER niacin (26 patients) ($p < 0.001$). Thereafter, differences did not reach statistical significance. The percent of patients reporting flushing decreased over the course of the study in both groups, and by the final visit, 33% and 44% of ER niacin- and IR niacin-treated patients, respectively, continued to report flushing. The total number of flushing episodes was significantly higher in patients treated with IR versus ER niacin (1095 versus 576; $p < 0.001$) (Figure 5).[14] Flushing tended to be intensified in patients taking ER niacin; however, this was not accompanied by an increase in discontinuation. Gastrointestinal disturbances, pruritus, and rash were not significantly different in either treatment group compared with placebo. Moreover, similar proportions of patients in the ER and IR niacin groups withdrew prematurely from the study because of adverse reactions considered related to the study drug ($n = 8$ and $n = 12$, respectively).[14]

A summary of the clinical trial data suggests that IR, ER, and SR niacin result in significant reductions in LDL-C and increases in HDL-C. SR niacin shows slightly greater LDL-C-lowering efficacy than IR niacin and appears to be less effective for raising HDL-C levels than IR niacin.[10,11] The pattern of adverse events suggests that SR niacin is associated with a significantly higher rate of aminotransferase elevations and gastrointestinal adverse effects compared with IR niacin. The lipid-modifying efficacy of ER niacin appears to be largely equivalent to IR niacin with a significantly lower inci-

Figure 4. Serum AST and ALT levels in 223 dyslipidemic patients treated with IR and ER niacin.[14] [a]$p < 0.001$ versus ER niacin. [b]IR niacin given at 3000 mg/day. AST = aspartate aminotransferase, ALT = alanine transaminase, ER = extended release, IR = immediate release, IU/L = international units per liter.

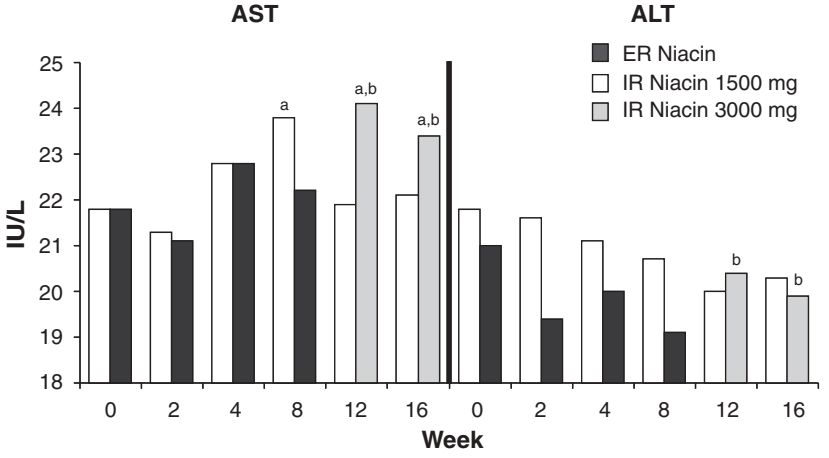
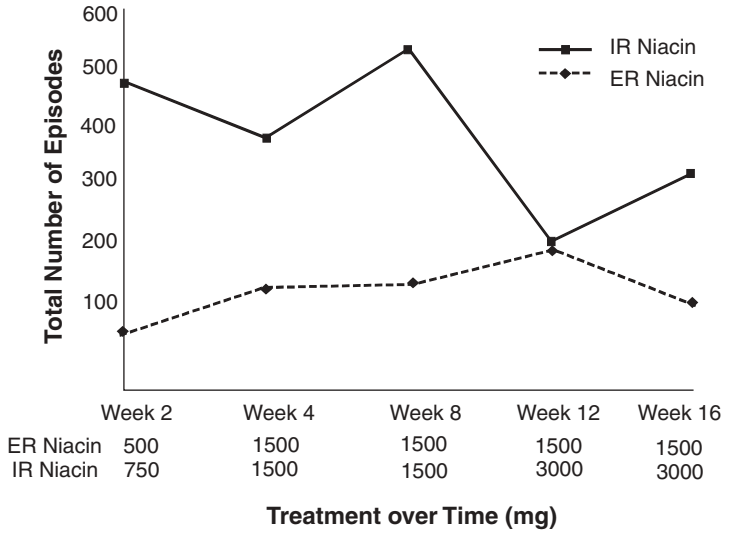


Figure 5. Total number of flushing episodes at each visit in dyslipidemic patients treated with IR and ER niacin over 16 weeks.[14] ER = extended release, IR = immediate release.



dence of flushing.[14] The ER formulation, then, appears to have fulfilled its promise as a niacin delivery strategy with equivalent efficacy and significantly fewer adverse effects compared to older IR and SR formulations, and with the added convenience of a once-a-day formulation.

Implications for the pharmacist

Several national organizations have released statements regarding the use of niacin.[17,18] The American Society of Health-System Pharmacists (ASHP) has released a position statement asking pharmacists to actively monitor patient selection of niacin products because of the various potentials for toxicity and states that pharmacists should discourage patients from self-treating with niacin.[17] Concerns have also been raised regarding the marketing of older, conventional agents as "nutritional supplements" rather than as prescription drugs. Such supplements are promoted as lipid-modifying agents, even though they are not FDA approved for this use and are sold in strengths far exceeding the recommended daily allowance for niacin.[11] ASHP also stresses the importance of treating serious conditions such as dyslipidemia under the direct supervision of a health care provider to monitor the efficacy and safety of the treatment. Furthermore, the guidelines state that pharmacists should not recommend SR niacin for the treatment of dyslipidemia.[17]

A position statement on the treatment of dyslipidemia from the Center for Drug Evaluation and Research (CDER) of FDA holds that drug treatments for dyslipidemia should not be sold over the counter in the United States.[18] Because treatment for lipid disorders requires accurate diagnosis and careful practitioner-directed medical management, CDER maintains that this can be ensured through prescription requirements and that over-the-counter medications should be reserved for symptomatic, easily recognizable conditions that are usually of short duration.[18]

The pharmacist should, therefore, be familiar with the available niacin formulations, and the benefits and adverse effects associated with each one. Pharmacists are in the unique position to educate individuals with dyslipidemia who are considering the use of niacin. When counseling patients, emphasis should be placed on maximizing the benefits of niacin under the supervision of a health professional and complying with therapy. Pharmacists can provide important advice and cautions concerning the safe use of niacin and monitor lipid and safety outcomes of niacin therapy. The strategies for minimizing flushing and increasing compliance that should be discussed whenever niacin is used include (1) take niacin with food (low-fat snack), (2) take 325 mg of aspirin approximately 45 to 60 minutes before the first dose of niacin,[17] and (3) avoid alcohol, hot showers, spicy

foods, and hot beverages soon after dosing.[13,17]

Pharmacists can also be a source of important guidance on recognizing the signs of more serious reactions such as hepatotoxicity (fatigue, jaundice, nausea, vomiting, and dark urine). For patients taking IR niacin who are experiencing intolerable flushing, pharmacists should not suggest over-the-counter SR niacin. If a switch to ER niacin is indicated, the pharmacist should ensure that the proper starting dose and titration schedule for the new agent is used.[17]

Conclusion

Niacin is a proven therapeutic option for the treatment of dyslipidemia. It is the only available agent that favorably affects all components of the lipid profile. Evidence suggests that ER niacin has efficacy comparable to that of IR niacin, with a significantly lower incidence of flushing and without the increased risk of elevated hepatic transferases associated with some of the SR niacin formulations. Efficacy and safety of niacin therapy, regardless of formulation used, are most likely maximized when carried out under the supervision of a health professional. Pharmacists can play an important role in the safe and effective use of niacin therapy by educating patients and health care providers about the differences among available formulations, advising on strategies for minimizing adverse effects like flushing, recognizing symptoms of hepatotoxicity, and monitoring cholesterol values.

References

1. Altschul R, Hoffer A, Stephen JD. Influence of nicotinic acid on serum cholesterol in man. *Arch Biochem Biophys*. 1955; 54:558-9. Letter.
2. Grundy SM, Mok HY, Zech L et al. Influence of nicotinic acid on metabolism of cholesterol and triglycerides in man. *J Lipid Res*. 1981; 22:24-36.
3. Piepho RW. The pharmacokinetics and pharmacodynamics of agents proven to raise high-density lipoprotein cholesterol. *Am J Cardiol*. 2000; 86(suppl):35L-40L.
4. Carlson LA, Hamsten A, Asplund A. Pronounced lowering of serum levels of lipoprotein Lp(a) in hyperlipidaemic subjects treated with nicotinic acid. *J Intern Med*. 1989; 226:271-6.
5. Jin F-Y, Kamanna VS, Kashyap ML. Niacin decreases removal of high-density lipoprotein apolipoprotein A-I but not cholesterol ester by Hep G2 cells: implication for reverse cholesterol transport. *Arterioscler Thromb Vasc Biol*. 1997; 17: 2020-8.
6. Kamanna VS, Kashyap ML. Mechanism of action of niacin on lipoprotein metabolism. *Curr Atheroscler Rep*. 2000; 2:36-46.
7. Superko HR, Krauss RM. Differential effects of nicotinic acid in subjects with different LDL subclass patterns. *Atherosclerosis*. 1992; 95:69-76.
8. The Coronary Drug Project Research Group. Clofibrate and niacin in coronary heart disease. *JAMA*. 1975; 231:360-81.
9. Canner PL, Berge KG, Wenger NK et al. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. *J Am Coll Cardiol*. 1986; 8:1245-55.
10. McKenney JM, Proctor JD, Harris S et al. A comparison of the efficacy and toxic effects of sustained- vs immediate-release niacin in hypercholesterolemic patients. *JAMA*. 1994; 271:672-7.
11. 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.
12. Knopp RH. Evaluating niacin in its various forms. *Am J Cardiol*. 2000; 86 (suppl):51L-6L.
13. Capuzzi DM, Morgan JM, Brusco OA, Jr. et al. Niacin dosing: relationship to benefits and adverse effects. *Curr Atheroscler Rep*. 2000; 2:64-71.
14. Knopp RH, Alagona P, Davidson M et al. Equivalent efficacy of a time-release form of niacin (Niaspan) given once-a-night versus plain niacin in the management of hyperlipidemia. *Metabolism*. 1998; 47: 1097-104.
15. Wilkin JK, Wilkin O, Kapp R et al. Aspirin blocks nicotinic acid-induced flushing. *Clin Pharmacol Ther*. 1982; 31:478-82.
16. Stern RH, Freeman D, Spence JD. Differences in metabolism of time-release and unmodified nicotinic acid: explanation of the differences in hypolipidemic action? *Metabolism*. 1992; 41:879-81.
17. American Society of Health-System Pharmacists. ASHP therapeutic position statement on the safe use of niacin in the management of dyslipidemias. *Am J Health-Syst Pharm*. 1997; 54:2815-9.
18. Center for Drug Evaluation and Research. Guidance for industry. OTC treatment for hypercholesterolemia. Rockville, MD: U.S. Food and Drug Administration; 1997.