Should liver enzymes be checked in a patient taking niacin?

EVIDENCE-BASED ANSWER

No randomized trials directly address the question of frequency of liver enzyme monitoring with niacin use. Niacin use is associated with early and late hepatotoxicity (strength of recommendation [SOR]: **B**, based on incidence data from randomized controlled trials and systematic reviews of cohort studies). Long-acting forms of niacin (Slo-Niacin) are more frequently associated with hepatotoxicity than the immediate-release (Niacor, Nicolar) or extended-release (Niaspan) forms (SOR: **B**, based on 1 randomized controlled trial and systematic reviews of cohort studies).

The combination of statins and niacin at usual doses does not increase the risk of hepatotoxicity (SOR: **A**, based on randomized controlled trials). Screening has been recommended at baseline, 6 to 8 weeks after reaching a daily dose of 1500 mg, 6 to 8 weeks after reaching the maximum daily dose, then annually (SOR: **C**, based on expert opinion).

EVIDENCE SUMMARY

Three forms of niacin exist: immediate-release (IR), sustained-release/long-acting (SR/LA), and extended-release (ER), which is currently available only as Niaspan.[1] Published incidence of niacin-induced hepatotoxicity varies according to the definition of hepatotoxicity, with a 0% to 46% rate of elevated hepatic enzymes. Hepatotoxicity includes mild liver enzyme elevations, steatosis, hepatitis, abnormal liver biopsies, or fulminant hepatic failure.[2,3] Between 1982 and 1992, 11 case reports have linked IR nicotinic acid to a wide range of hepatotoxicities. For patients taking LA/SR niacin doses ≥3 g/d or switching from the IR to the LA product, 21 case reports have linked LA/SR niacin with adverse outcomes.[3,4] In several of the LA/SR cases, patients were rechallenged with IR formulations with no recurrent hepatocellular damage.[3,4] In these case reports, onset of hepatotoxicity ranged from 2 days to 18 months. In a retrospective cohort of 969 veterans taking LA/SR niacin, those who developed hepatotoxicity had onset between 1 and 28 months of initiating treatment.[2] Studies evaluating the risk of hepatotoxicity with niacin alone and in combination with statins are summarized in the **Table**.

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What are Clinical Inquiries?

Clinical Inquiries answer recent questions from the practices of family physicians. Practicing family physicians choose the most relevant questions submitted through a web-based voting system operated by the Family Physicians Inquiries Network (FPIN; online at www.fpin.org).

FPIN is national, not-for-profit consortium of family medicine departments, community residency programs, academic health sciences libraries, primary care practice-based research networks, and other specialists. Once questions are selected, FPIN editors then organize teams of clinicians and librarians to answer them based on systematic review of the world literature.

Answers are developed through an explicit, systematic method:

- FPIN librarians and editors identify questions recently answered in best evidence sources (e.g. Cochrane Reviews, Clinical Evidence, the US Preventive Services Task Force, Evidence Based Guidelines, a published systematic review).
- FPIN librarians then conduct systematic and standardized literature searches of best evidence sources, Medline, and other databases in collaboration with an FPIN clinician or clinicians. If a best evidence source has been identified, the search begins from the date of the search conducted for that source. Otherwise, the searches are comprehensive.
- FPIN clinician authors then choose the highest quality original research sources, and critically appraise the research and integrate the findings in the Evidence Based Answer and Evidence Summary section of Clinical Inquiries. Authoritative sources are also quoted in the "Recommendations from Others" section of the Clinical Inquiry.
- Each Clinical Inquiry is reviewed by 4 or more peers or editors before publication in *JFP*.
- FPIN medical librarians are accountable for the thoroughness of the literature search, for recording the databases searched, search hedges used and the search terms. The details of each search is available to any interested reader (contact managingeditor@fpin.org).
- Finally, a practicing family physician or other clinician writes an accompanying commentary to provide a clinical perspective.

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TABLE

Studies of niacin toxicity

Author, evidence	Pts/duration of Rx	Lipid therapy	Hepatotoxicity
Gray,[2] retrospective cohort	896 pts/ 1–3 mos	LA/SR (Slo-Niacin) avg 1500 mg/d	2.2% probable, 4.7% possible or probable
Capuzzi,[6] open-label, prospective	517 pts/ ≤96 wks	ER (Niaspan) 1000–3000 mg/d	<1% w/ transaminases >3 times ULN
McKenney,[5] randomized, double-blind, placebo-controlled	46 pts/ 30 wks	LA/SR niacin or IR niacin: titrated from 500 mg/d to 3000 mg/d	52% SR pts with ↑ transaminases (78% SR pts withdrew); 0% IR pts with ↑ transaminases
Grundy,[9] randomized, double-blind, placebo-controlled	97 pts/ 16 wks	ER (Niaspan) 1000–1500 mg/d	0% with transaminases >3 times ULN
Zhao,[10] randomized, double-blind, placebo-controlled	80 pts/ 38 mos	LA/SR niacin (Slo-Niacin) 250 mg twice daily titrated to 1000 mg twice daily or switched to IR (Niacor) titrated to 3000–4000 mg/d + simvastatin 10 mg/d titrated to maintain LDL-C	3% w/transaminases >3 times ULN (transient—resolved with temporary halt or decrease in med)
Parra,[3] randomized, double-blind	74 pts/ 9 wks	IR niacin titrated to max of 3000 mg/d + fluvastatin 20 mg/d	0% with transaminases >3 times ULN
Davignon,[11] randomized, placebo-controlled	168 pts/ 96 wks	LA/SR niacin (Nicobid) 1000 mg twice daily vs Nicobid 1000 mg twice daily + pravastatin 40 mg nightly	3% > 3 times baseline transaminases (Nicobid alone) vs 1.2% >3 times baseline transaminases (Nicobid + pravastatin)

LA/SR, long-acting/sustained release; IR, immediate release; ER, extended release; ULN, upper limit of normal; LDL-C; low-density lipoprotein cholesterol.

Because LA/SR niacin has an active metabolite (nicotinamide), hepatotoxicity is more likely to occur with the LA/SR formulation than with IR niacin.[3] In a small prospective comparative study of IR and LA/SR niacin (n=46), 0/23 patients taking IR niacin exhibited hepatic toxicity, compared with 12/23 (52%) of patients taking the LA/SR formulation.[5] In this study, patients receiving 1 g/d of LA/SR niacin had increases in transaminases similar to those of patients on 3 g/d of IR niacin. It is therefore recommended that if a patient cannot tolerate IR niacin and is switched to the LA/SR form, the dosage be reduced by 50% to 70%.[5] At doses >2 g/d of LA/SR niacin, mean transaminases approached 3 times the upper limit of normal (ULN), supporting recommendations not to exceed this dose for LA/SR niacin.[5]

Several LA/SR products exist, and their differing pharmacologic and clinical properties necessitate monitoring as though starting anew when changing from one LA/SR formulation to another.[1] Because of the unfavorable risk-benefit ratio of LA/SR formulations compared with other niacin formulations, production and marketing of many

LA/SR niacin brands has ceased. The ER formulation (Niaspan), only available by prescription, has a balanced metabolism resulting in less hepatotoxicity (<1%).[1,6] Expert opinion mandates continued annual monitoring of liver function tests (LFT) for all patients, including those on a stable ER niacin dose, no new risk factors for hepatotoxicity, and a series of normal LFTs.[7]

RECOMMENDATIONS FROM OTHERS

Elevated hepatic enzymes <3 times the ULN may occur but usually resolve with continued therapy or reduced doses. Enzymes >3 times the ULN require discontinuation of therapy.[8] The American Society of Health-System Pharmacists (ASHP) recommends screening at baseline, every 2 to 3 months for the first year and every 6 to 12 months thereafter.[8] The ASHP also recommends that patients be started on IR niacin products, with consideration of ER products only when IR products are not tolerated or alternative products are ineffective. ASHP makes no mention of LA/SR products in their recommendations.[8] They recommend more frequent monitoring for high-risk patients—risks include doses >2 g/d for LA/SR and >3 g/d for IR; LA/SR formulations; switching between formulations; taking concomitant drugs that interact (ie, sulfonylureas); excessive alcohol use (undefined); and preexisting liver disease (based on a bivariate analysis of factors associated with increased risk of hepatic toxicity from a single retrospective cohort study)[5]—and for patients who demonstrate signs/symptoms of toxicity (nausea, vomiting, malaise, loss of appetite, right upper quadrant pain, jaundice, and dark urine).[8] The National Cholesterol Education Program Expert Panel update in 2004 recommended obtaining ALT/AST initially, 6 to 8 weeks after reaching a daily dose of 1500 mg, 6 to 8 weeks after reaching the maximum daily dose, then annually or more frequently if indicated.[7]

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CLINICAL COMMENTARY

Risk of toxicity with long-acting niacin is significant enough to avoid use

Our clinical experience is that once our patients are on stable doses of most medicines and have had a series of normal lab tests, we are unlikely to find toxicities from continued routine testing. That appears to be the case with niacin and liver toxicity, but long-term data are lacking for asymptomatic late reactions to usual niacin doses. The risk of toxicity with "long-acting" forms of niacin is significant enough that I see no reason to use them at all. If one wants to save money, use IR niacin. If cost is not an issue or regular niacin is not tolerated, I use the ER Niaspan. Both of these forms have very low rates of liver toxicity.

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How useful is high-sensitivity CRP as a risk factor for coronary artery disease?

EVIDENCE-BASED ANSWER

Little evidence supports the use of the high-sensitivity C-reactive protein assay (hs-CRP) as a screening test for cardiovascular disease (CVD) in the healthy adult population. There is significant debate about its use in populations at moderate risk for cardiovascular disease, with some evidence suggesting its use if the results of the test will alter treatment recommendations[1] (strength of recommendation [SOR]: **C**, based on extrapolation of consistent level 2 studies). Research to date is inadequate to determine the role of hs-CRP in risk-stratification of patients when considered in light of other standard risk factors (**Table**).

EVIDENCE SUMMARY

C-reactive protein is a nonspecific serum marker of inflammatory response. While it is elevated in a variety of conditions, a link has been suggested between CRP and pathogenesis of clinical cardiovascular disease.[1]

Several retrospective studies have reported risk ratios for developing cardiovascular disease, ranging from 2.3 to 4.4 when comparing subjects with the highest levels of hs-CRP with those who have the lowest levels.[2–9] Though systematic bias in retrospective study design limits the interpretation of these findings, the findings are of some benefit to answering this question when large, prospective, randomized studies are not available.

One of the largest and most recent of these studies reports adjusted odds for development of coronary artery disease of 1.45 (95% confidence interval [CI], 1.25–1.68) for subjects in the top third of hs-CRP levels compared with those in the bottom third.[9] Odds ratios (OR) for other predictors of coronary artery disease are higher than this, in particular total cholesterol (OR=2.35; 95% CI, 2.03–2.74), cigarette smoking (OR=1.87; 95% CI, 1.62–2.22), and elevated systolic blood pressure (OR=1.50; 95% CI, 1.30–1.73). This shows that hs-CRP does not contribute as much as these factors to the established risk profile for coronary heart disease.

These same authors go on to provide a systematic review of 22 prospective studies of hs-CRP involving 7068 patients, which showed that an elevated hs-CRP was associated with higher odds of developing coronary artery disease (OR=1.58; 95% CI, 1.48–1.68). They also examined the largest 4 studies in their review (which included 4107 cases) and found a slightly lower OR of 1.49 (95% CI, 1.37–1.62). This meta-analysis included only studies published since 2000 because earlier studies, which had yielded higher odds for hs-CRP, suggested a pattern consistent with publication bias.

Two very recent studies evaluating statin therapy for CVD suggest that CRP may be monitored as an independent factor for predicting CVD outcomes for patients undergoing aggressive lipid therapy.[10,11] These randomized, masked trials suggest that CRP is directly predictive of recurrent events among patients with known CVD. Its usefulness may be greatest when trying to decide whether to pursue aggressive (high-dose) statin therapy for these patients.

It is not clear whether hs-CRP is a direct, causative marker for atherosclerosis or whether it is simply a proxy marker elevated in conjunction with other known risk factors. This issue, combined with the fact that its elevation does not contribute as significantly as other risk factors, makes hs-CRP an inappropriate screening test for cardiovascular disease in the healthy adult

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