

Hepatitis Caused By Low-Dose Sustained-Release Niacin

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Professional and public education about the importance of cholesterol reduction in the prevention of heart disease has been extraordinarily successful in sensitizing patients to this important approach to cardiac risk factor reduction.¹ This educational campaign has raised patient awareness not only about the importance of cholesterol reduction but also about specific dietary and pharmacologic approaches to reduction. In particular, patient self-administration of over-the-counter (OTC) nicotinic acid or niacin preparations has become common. The practice of self-administration of niacin has the potential of causing serious drug-induced adverse effects if it is taken without the guidance of the patient's primary care physician.

Niacin is available in two forms, crystalline (short-acting) and sustained release. Cases have been reported of self-administered dosages of OTC crystalline niacin in the range of 3.0 to 4.5 g causing moderately severe (peak alanine aminotransferase [ALT] 3300 IU/L) drug-induced hepatitis.² Fortunately, the strength of OTC crystalline niacin preparations is relatively low (e.g., 500 mg) compared with the daily dosages generally prescribed by physicians (e.g., 1.5 to 7.5 g), so serious hepatic toxicity from OTC self-administration is unlikely. Patients are often aware, however, of the potential for unpleasant, albeit minor, side effects of crystalline niacin, particularly cutaneous flushing and nausea, and purposely select sustained-release preparations to minimize these side effects. The risk of cutaneous flushing, for example, is markedly less with sustained-release compared with crystalline preparations. It is not generally known to patients, as well as to many physicians, however, that sustained-release preparations of niacin have a risk of causing hepatitis at

dosage levels far lower than that reported for crystalline niacin, probably on an idiosyncratic rather than a dose-response basis.³

We present a case of hepatitis caused by self-administration of sustained-release niacin to illustrate the importance, when taking routine medical histories, of physicians asking about self-administered vitamin and medication use by patients.

Case Report

A 36-year old man came to the Family Practice Center complaining of a 1-week history of frontal headache, nausea, and fatigue. His headache was persistent but not associated with vomiting or vision changes. He was using ibuprofen every 4 hours with only moderate relief. He described his fatigue as "extreme" and had spent the previous 2 days in bed. He denied fever, diarrhea, abdominal pain, appetite change, previous blood transfusions, intravenous drug use, or high-risk sexual practices. He was a nonsmoker, and his consumption of alcohol consisted of approximately 4 beers a month. He had visited several European cities about 15 months earlier. His medical history was positive for longstanding obesity and sleep apnea. He had been using continuous positive airway pressure for more than 1 year with some relief of sleeplessness but continued to have moderate fatigue despite regular use.

His history was positive for hyperlipidemia, and a recent lipoprotein profile showed a total cholesterol of 241 mg/dL, triglycerides 222 mg/dL, high-density lipoprotein (HDL) 27 mg/dL, and low-density lipoprotein (LDL) 176 mg/dL. An appropriate diet, weight loss, and exercise program had been recommended in response to his lipoprotein profile, but the patient had been unable to make some of these changes. His psychosocial and family history revealed increased stress secondary to a pending divorce from his wife of 12 years. He had received notice of the final court date for divorce settlement 2 days before the onset of his symptoms.

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In addition to the attempted diet and exercise changes, but without the knowledge of his physician, the patient had chosen to treat his hyperlipidemia with an OTC sustained-release niacin preparation of 500 mg daily for the past 2 years. The most recent OTC brand of niacin taken for the last few months was Your Life (P. Leiner Nutritional Products, Inc., Torrance, California), but different brands of sustained-release niacin were used during the preceding 2 years. The use of these niacin products was not immediately volunteered by the patient but was revealed upon repeat questioning by his nurse practitioner.

On physical examination the patient was an obese, pale, slightly diaphoretic man with a flat affect. He was nonicteric, he had no organomegaly, and the examination was otherwise unremarkable. Laboratory examination showed a mild anemia with a hemoglobin of 13.7 mg/dL and hematocrit of 40.3 percent. His liver function tests (Table 1) showed a peak total aspartate aminotransferase (AST) of 408 U/L, ALT of 771 U/L, lactic acid dehydrogenase (LDH) of 564 U/L, and alkaline phosphatase of 291 U/L. Serologic studies for hepatitis, including antihepatitis A, hepatitis B surface antigen and antibody, hepatitis B_e antigen, and antihepatitis C, were negative. A screening test for infectious mononucleosis was negative, and his prothrombin time at 11.7 sec was normal. Based upon a lack of risk factors for infectious hepatitis, and the results of an immediate search of the relevant literature while the patient was in the office, a working diagnosis of niacin-induced hepatitis was made. The niacin was discontinued, and symptomatic care was provided.

Discontinuing the niacin resulted in gradual clinical improvement. Six days after stopping the

niacin he felt some improvement in appetite and energy level. His liver function tests showed gradual normalization during the next 5 weeks. Within 2 weeks of discontinuation of the niacin, he complained of "tiring easily" but reported improved energy and appetite. Approximately 1 month later he reported "some fatigue" but felt much better. He was able to return to work in the interim. Subsequent cholesterol testing at 8 weeks after stopping the niacin showed a total cholesterol of 244 mg/dL, triglycerides 334 mg/dL, HDL 27 mg/dL, and LDL 161 mg/dL. Further decisions regarding treatment of his hyperlipoproteinemia excluded niacin as a possible choice.

Discussion

The association of hepatic toxicity with sustained-release forms of niacin was first reported more than 30 years ago,⁴ but this association has received little attention from either patients or physicians. The National Cholesterol Education Program and other treatment guidelines do not distinguish between crystalline and sustained-release preparations,^{1,5} and most discussions suggest that niacin toxicity in general is associated only with dosages greater than 3 g/d,⁶ although presumably these guidelines refer to crystalline niacin. This case is similar to those reported previously with regard to the severity of hepatitis caused by the sustained-release form of niacin,³ although occasional reports describe severe hepatitis with massive lobular collapse and marked cholestasis seen on liver biopsy. The time course of 2 years in the development of hepatitis is also consistent with past reports, but some patients have developed hepatitis within 7 weeks of starting sustained-release niacin.³ Presumably our patient did not have abnormal liver function tests for the entire 2-year time, but the beginning of his actual illness cannot be determined. The mechanism of injury in hepatitis caused by sustained-release niacin is not fully understood, and there are no known patient characteristics that predispose to hepatic injury. The mechanism appears to be idiosyncratic or immunologic, rather than a direct toxic effect, because patients previously suffering hepatitis from sustained-release niacin can be challenged with crystalline niacin without a recurrence of hepatitis.⁷ The patient described here was not willing to consider such a challenge after suffering from the ill effects of sustained-

Table 1. Serial Tests for Liver Function (U/L).

Date	AST*	ALT	LDH	Alk Phos
25 June 1992	356	556	516	156
27 June 1992†	408	771	564	258
2 July 1992	229	556	438	291
10 July 1992	65	127	368	152
27 July 1992	33	47	190	69

*AST=aspartate transaminase (normal 2-35 U/L), ALT=alanine transaminase (normal 0-45 U/L), LDH=lactic acid dehydrogenase (normal 60-200 U/L), Alk Phos=alkaline phosphatase (normal 30-130U/L).

†Niacin discontinued.

release niacin, and he was emphatic about his desire never to take niacin again. He was equally emphatic about not taking any OTC preparations, whether vitamin or medication, without consulting his physician.

This case of hepatitis caused by sustained-release niacin highlights the following important points in the care of hyperlipoproteinemic patients: (1) patients have a high level of interest and knowledge about the importance of treating hypercholesterolemia, and they will sometimes pursue OTC remedies without the guidance of a physician; (2) crystalline and sustained-release niacin both cause hepatitis but at different dosages and probably by different mechanisms; (3) the development of hepatitis caused by sustained-release niacin usually takes several months but can develop much more quickly; and (4) the hepatitis caused by sustained-release niacin is usually self-limited, although massive hepatic damage is possible. Physicians should, of course, be attentive to all medication and vitamin self-administration

but particularly so to such potentially toxic OTC medications as sustained release niacin.

References

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