Niacin-Induced Clotting Factor Synthesis Deficiency With Coagulopathy

Brian D. Dearing, MD; Carl J. Lavie, MD; Thomas P. Lohmann, MD; Edward Genton, MD

- Although coagulopathy is a well-known complication of severe niacin-induced hepatotoxic reaction, it is not found in patients with minimal aminotransferase level elevations. Three patients with significant clotting factor synthesis deficiency and coagulopathy (prothrombin times, >1.5 times control) from sustained-release niacin had only mild aminotransferase level elevations (1.5 to 2.0 times normal). In each case, protein deficiency, coagulopathy, and aminotransferase level elevation resolved promptly after withdrawal of niacin therapy. In one case, this syndrome recurred after rechallenge with sustained-release niacin, whereas the coagulopathy did not recur in a second patient rechallenged with crystalline niacin. Deficiency in protein synthesis, including coagulation factors, and coagulopathy are unrecognized complications of sustained-release niacin therapy. These cases indicate the need to measure prothrombin times routinely in patients who develop even mild aminotransferase level elevation while receiving sustained-release niacin therapy. These data are important in light of the increasing use of sustained-release niacin in the treatment of patients with lipid disorders. (Arch Intern Med. 1992;152:861-863)

During the past two decades, the lipid–coronary heart disease (CHD) hypothesis has become better established. Therefore, greater efforts are being directed at both nonpharmacologic and drug treatment of lipid disorders, particularly elevated levels of total cholesterol and low-density lipoprotein cholesterol.1 Epidemiologic, lipid intervention, and coronary angiographic studies have also documented the pivotal role of high-density lipoprotein cholesterol for assessing CHD risk, with considerable data suggesting that this lipoprotein may be the best lipid predictor of CHD.2-10

Niacin (nicotinic acid), a water-soluble B vitamin, may be an ideal lipid-lowering agent, since it is relatively inexpensive and has beneficial effects in most patients with dyslipemias. Niacin therapy has been shown to be associated with reduced CHD events and reduced progression of coronary artery disease by angiography.11,12 and it is the only lipid-lowering drug to be associated with long-term reduction in total mortality.4,5 Its mechanism of action is not completely understood, but it significantly reduces levels of total cholesterol, low-density lipoprotein cholesterol, and triglycerides as well as increases the level of high-density lipoprotein.1-3,13 The hypolipidemic effect is thought to result from a decrease in synthesis of very-low-density lipoprotein particles (which are formed in hepatocytes and from which low-density lipoprotein cholesterol is derived) and inhibition of stimulation of lipolysis.14 Although niacin therapy may be limited by troublesome short-term adverse effects, they are usually not life threatening, and the long-term safety is well established. Sustained-release preparations of niacin decrease the incidence of side effects and improve compliance and, therefore, are becoming more popular. While niacin therapy has been associated with hepatotoxic effects,15-25 there is no documentation of niacin-induced alterations in clotting factor synthesis or coagulopathy without significant hepatotoxic effects. In the present report, we present three cases of niacin-induced significant coagulopathy secondary to clotting factor deficiency, with minimal evidence of hepatotoxic reaction.

REPORT OF CASES

CASE 1.—A 55-year-old man with known coronary artery disease and hyperlipidemia presented with crescendo angina. Medications at the time of admission included sustained-release diltiazem hydrochloride, 90 mg twice a day; aspirin once a day; and sustained-release niacin, 1000 mg twice a day (which had been started 3 months earlier).

Admission laboratory tests revealed a coagulopathy (prothrombin time [PT] of 17.2 seconds with a control of 11.3 seconds) with minimal aminotransferase level elevation (Table). Mixing studies disclosed a factor deficiency. The niacin was discontinued, and the prothrombin time slowly improved. Results of laboratory tests repeated 14 days later were normal. The patient was rechallenged with niacin, 500 mg twice a day for 1 week, then 1000 mg twice a day; 11 days later, his PT was 19.3 seconds (control, 11.3 seconds). The niacin was again discontinued, and after 5 days his PT and liver enzyme levels were normal.

CASE 2.—A 47-year-old man with coronary artery disease, hyperlipidemia, and a remote history of inactive non-A, non-B hepatitis presented with unstable angina pectoris. Medications
Laboratory Values in Three Patients With Niacin-Induced Clotting Factor Synthesis Deficiency and Coagulopathy*

<table>
<thead>
<tr>
<th></th>
<th>Albumin, g/L</th>
<th>Total Bilirubin, μmol/L</th>
<th>AST, U/L</th>
<th>ALT, U/L</th>
<th>TC, mmol/L (mg/dL)</th>
<th>TG, mmol/L (mg/dL)</th>
<th>HDL-C, mmol/L (mg/dL)</th>
<th>PT, s</th>
<th>PTT, s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal values</td>
<td>35-55</td>
<td>1.7-17.1</td>
<td>0-37</td>
<td>0-40</td>
<td>3.10-5.15</td>
<td>0.63-3.15</td>
<td>0.98-1.63</td>
<td>11.3</td>
<td>29.8</td>
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<td>Patient 1</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>47</td>
<td>17.1</td>
<td>22</td>
<td>28</td>
<td>6.00 (232)</td>
<td>1.14</td>
<td>1.16 (45)</td>
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<tr>
<td>Acute presentation§</td>
<td>35</td>
<td>10.3</td>
<td>55</td>
<td>86</td>
<td>3.96 (153)</td>
<td>0.40</td>
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<tr>
<td>Recovery§</td>
<td>45</td>
<td>8.6</td>
<td>19</td>
<td>17</td>
<td>5.69 (220)</td>
<td>0.75</td>
<td>1.16 (45)</td>
<td>12.2</td>
<td>24.9</td>
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<td>Rechallenge¶</td>
<td>. . .</td>
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<td>. . .</td>
<td>. . .</td>
<td>19.3</td>
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<td>Patient 2</td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>Baseline</td>
<td>47</td>
<td>12.0</td>
<td>65</td>
<td>56</td>
<td>1.66 (64)</td>
<td>0.59</td>
<td>1.2</td>
<td>19.2</td>
<td>36.8</td>
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<tr>
<td>Acute presentation¶</td>
<td>32</td>
<td>10.3</td>
<td>17</td>
<td>15</td>
<td>4.63 (179)</td>
<td>1.32</td>
<td>0.65 (25)</td>
<td>11.4</td>
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<tr>
<td>Recovery¶</td>
<td>44</td>
<td>15.4</td>
<td>31</td>
<td>37</td>
<td>5.20 (201)</td>
<td>0.89</td>
<td>1.01 (39)</td>
<td>11.9</td>
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<td>Patient 3</td>
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<tr>
<td>Baseline</td>
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<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
<td>17.7</td>
<td>33.1</td>
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<tr>
<td>Acute presentation**</td>
<td>38</td>
<td>12.0</td>
<td>73</td>
<td>56</td>
<td>2.97 (115)</td>
<td>0.41</td>
<td>. . .</td>
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<tr>
<td>Recovery§</td>
<td>47</td>
<td>12.0</td>
<td>18</td>
<td>18</td>
<td>4.14 (160)</td>
<td>0.93</td>
<td>0.57 (22)</td>
<td>12.6</td>
<td>27.6</td>
</tr>
</tbody>
</table>

*ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; HDL-C, high-density lipoprotein cholesterol; PT, prothrombin time; PTT, partial thromboplastin time; TC, total cholesterol; and TG, triglycerides.

†Control mean.
§Slo-Niacin, 1000 mg twice daily for 3 months.
¶All follow-up laboratory work 2 to 3 weeks after discontinuing niacin.
||Slo-Niacin, 1000 mg twice daily for 2 weeks.
§§SR-Niacin, 1000 mg three times daily for 10 months.
#Crystalline niacin, 1000 mg twice daily for 3 months.
**Slo-Niacin, 1000 mg three times daily for 5 weeks.

at this time included one aspirin tablet daily and sustained-release niacin, 1000 mg twice a day.

Initial laboratory tests (Table) revealed mild aminotransferase level elevation with a coagulopathy (PT, 19.2 seconds with a control of 11.5 seconds). An abdominal computed tomographic scan was performed to exclude malignant neoplasm, in light of low plasma cholesterol and albumin levels; the hepatic size was normal, with homogeneous parenchyma.

The niacin was discontinued and phytodnabine was administered; the PT normalized over approximately 2 days. Follow-up laboratory values were within normal limits. The subject was then rechallenged with crystalline niacin and, after 4 months, had not developed any laboratory abnormalities.

Case 3.—A 44-year-old man with known coronary artery disease presented with exertional angina. His medications at the time of admission were sustained-release diltiazem hydrochloride, 120 mg twice a day; aspirin once a day; and sustained-release niacin, 1000 mg three times a day (for 5 weeks).

Laboratory studies at admission (Table) disclosed a coagulopathy (PT, 17.7 seconds with a control of 11.3 seconds), again with only mild aminotransferase level elevation. Qualitative factor assays obtained during the acute presentation demonstrated markedly decreased factor VII (20%) and borderline decreased factor II (5%) levels but normal factor IX and X levels. Quantitative immunologic factor assay showed a proportional reduction in the level of factor VII (14%).

The niacin was discontinued, and the laboratory values returned to normal. Functional factor assays repeated at 2 weeks demonstrated a mildly reduced factor VII level of 40% and a normal factor II level of 92%.

COMMENT

The incidence and mechanism of niacin-induced hepatotoxic reaction are not known.15-20 Biopsy specimens have demonstrated cholestatic changes with cell necrosis and portal fibrosis.16 Fulminant hepatic failure may rarely occur with niacin treatment.17,18 Typically, significant hepatotoxic reaction occurs with high doses (>3 g/d) given for prolonged periods,16 indicating a need for monitoring aminotransferase values in patients receiving niacin therapy.2 In niacin-treated patients with hepatotoxic reactions, it is not unusual to find markedly prolonged PTs,16-20 but this coagulopathy is associated with a greater than threefold elevation in hepatic aminotransferase values and a greater than twofold elevation in bilirubin levels. In the present cases, however, the coagulopathy occurred out of proportion to the aminotransferase level elevation (Table) and without hyperbilirubinemia, but it was associated with reduced levels of albumin and lipoproteins. This is an important observation, since it is common to monitor only the aminotransferase values after initiating niacin therapy, and a mild elevation in such a nonspecific test may not suggest significant drug-induced toxic reaction.

The mechanism of this niacin-induced coagulopathy is not clear and may represent a different pathophysiology than that of typical niacin-induced hepatitis. The associated laboratory abnormalities (Table), such as decreased albumin levels and markedly decreased levels of plasma cholesterol and triglycerides, with mildly elevated aminotransferase values, suggest a mechanism of decreased synthesis47 rather than hepatocellular injury. The quantitative decrease in factor VII level seen in patient 3 is also consistent with altered protein synthesis and establishes that the effect is not from qualitative changes in clotting factors, as is seen with vitamin K deficiency or warfarin therapy. It is not known if this is secondary to effects on

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hepatocyte secretion or a more basic biochemical mechanism affecting protein synthesis. In addition, our patients were all taking moderate doses (>2 g/d) of a sustained-release formula of niacin at the time of presentation, and patient 2 was rechallenged with crystalline niacin without recurrence of the coagulopathy. This raises the question of whether this phenomenon is secondary to nicotinic acid or is peculiar to the sustained-release preparation.

National attention is currently directed at lipids, and recent evidence suggests that low levels of high-density lipoprotein cholesterol are the predominant lipid abnormality in most patients with CHD. In addition, preliminary data indicate that sustained-release niacin therapy is extremely effective in patients with CHD who have "isolated" low levels of high-density lipoprotein cholesterol. These factors make it likely that the use of niacin therapy will increase. Our data suggest that prothrombin times should be monitored in patients who develop even mild aminotransferase level elevations or depressed lipoprotein levels while taking sustained-release preparations of niacin. The recognition of this coagulopathy in patients with trivial to mild aminotransferase level elevation is important, since, according to the manufacturer, niacin may activate peptic ulcer disease, and cardiac patients taking this drug are at risk for invasive vascular procedures. Also, patients taking oral anticoagulants should be closely monitored for markedly prolonged prothrombin times, since this abnormality may potentiate the effect of the drug.

Further studies will be required to determine the prevalence and exact mechanism of this niacin-induced clotting factor synthesis deficiency and coagulopathy, as well as the relative risk with the use of various niacin preparations. Also, the issue of selective vs general alteration of clotting factors and protein synthesis needs to be clarified.

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References


10. Lavie CJ, Mailander L, Milani RV. Marked benefit with niacin therapy in coronary patients with 'isolated' very low levels of high-density lipoprotein cholesterol. Circulation. In press.


