Antinuclear antibody-positive ticlopidine-induced hepatitis

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Ticlopidine hydrochloride has been shown to reduce the risk of first or recurrent stroke in patients who have experienced a transient ischemic attack, reversible ischemic neurological deficit, recurrent stroke or first stroke. Severe liver dysfunction is a contraindication for its use. Increase in liver enzymes has been reported with use of this drug, but jaundice is rare. A case of severe ticlopidine-induced hepatitis that was associated with a marked increase in antinuclear antibody (ANA) levels is reported. Physicians prescribing ticlopidine hydrochloride should be aware that a potentially severe acute hepatitis associated with ANA positivity can occur. The drug should be discontinued if signs of liver dysfunction occur.

Key Words: Adverse effect, Antinuclear antibody, Hepatitis, Ticlopidine

There was no history of liver disease and he had never received a blood transfusion. Family history for liver disease was negative. He only consumed alcohol on rare occasions. The only other medication he had been taking was alprazolam 0.25 mg/day.

He was started on ticlopidine 250 mg tid to prevent recurrent strokes. On day 35 he started to feel generally unwell, developed nausea and loss of appetite. He noticed that his urine became dark. Ticlopidine was stopped on day 38. On physical examination he was markedly jaundiced. No stigmata of chronic liver disease were present apart from Dupuytren’s contractures in both hands. There was no asterixis. The liver edge was just palpable below the costal margin and slightly tender. The rest of the physical examination was unremarkable except for slight loss of power in the right arm and leg.

Results of blood work are shown in Table 1. ANA showed...
Results of blood work

<table>
<thead>
<tr>
<th></th>
<th>Day</th>
<th>0</th>
<th>35</th>
<th>38</th>
<th>44</th>
<th>60</th>
<th>78</th>
<th>118</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST</td>
<td>(n&lt;31 U/L)</td>
<td>25</td>
<td>206</td>
<td>217</td>
<td>96</td>
<td>27</td>
<td>29</td>
<td>13</td>
</tr>
<tr>
<td>ALT</td>
<td>(n&lt;42 U/L)</td>
<td>29</td>
<td>497</td>
<td>511</td>
<td>283</td>
<td>44</td>
<td>34</td>
<td>16</td>
</tr>
<tr>
<td>ALP</td>
<td>(n&lt;104 U/L)</td>
<td>102</td>
<td>521</td>
<td>651</td>
<td>696</td>
<td>179</td>
<td>148</td>
<td>69</td>
</tr>
<tr>
<td>GT</td>
<td>(n&lt;40 U/L)</td>
<td>29 –</td>
<td>1119</td>
<td>838</td>
<td>322</td>
<td>105</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>Bill total</td>
<td>(n&lt;16 mol/L)</td>
<td>14</td>
<td>123</td>
<td>128</td>
<td>50</td>
<td>22</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Bill direct</td>
<td>(n&lt;10 mol/L)</td>
<td>2</td>
<td>61</td>
<td>68</td>
<td>4</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>ANA titre</td>
<td>– –</td>
<td>&gt;1:1600</td>
<td>1:400</td>
<td>1:100</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**TABLE 1**

<table>
<thead>
<tr>
<th>ALP Alkaline phosphatase</th>
<th>ALT Alanine aminotransferase</th>
<th>ANA Anti-nuclear antibody</th>
<th>AST Aspartate aminotransferase</th>
<th>Bill Bilirubin</th>
<th>GT Gamma glutamyl transferase</th>
</tr>
</thead>
</table>

a homogeneous pattern. Complete blood count, erythrocyte sedimentation rate, total eosinophil count, prothrombin time, partial thromboplastin time, total protein and albumin were normal. Hepatitis A serology was immunoglobulin (Ig) G-positive and IgM-negative. Hepatitis B and C serology and monospot were negative. Hepatitis C serology repeated after 18 months was still negative. Abdominal ultrasound of the liver, biliary tree and pancreas was normal. A liver biopsy was not performed.

Without specific treatment the patient recovered completely. Jaundice resolved, liver enzymes returned to normal and the ANA became negative over the following 12 weeks. All liver blood work remained normal over the following 18 months.

**DISCUSSION**

We believe that this patient suffered from ticlopidine-induced acute hepatitis and that it was associated with transient ANA positivity. We believe that this is the first reported case of ticlopidine-associated ANA-positive acute hepatitis because a recent MEDLINE search retrieved no other such cases. The patient’s hepatitis was severe but reversible after the medication was discontinued. He had no risk factors for viral hepatitis. Hepatitis C serology, repeated after 18 months and still negative, was done to rule out the possibility that the patient had an acute hepatitis C infection and had not yet developed antibodies.

Alprazolam as a cause of ticlopidine-associated ANA-positive acute hepatitis seems unlikely because the patient had not been rechallenged with alprazolam. We are unaware of any reports of alprazolam-induced hepatitis. We recently became aware of another case of acute hepatitis in a 73-year-old woman that occurred four weeks after ticlopidine 250 mg tid was started. Maximum enzyme levels were alanine aminotransferase 728 U/L, aspartate aminotransferase (AST) 348 U/L, alkaline phosphatase 448 U/L and total bilirubin 52 U/L, but ANA was not determined. Liver enzyme abnormalities completely resolved by three weeks after ticlopidine discontinuation.

Most patients treated with ticlopidine hydrochloride show some increase above baseline in their levels of alkaline phosphatase, and the increase exceeded the upper range of normal in approximately one-third of patients (3). In 6% of patients, the value was more than twice the upper reference limit (3). The maximum rise, which is generally asymptomatic, occurs at one to four months of therapy and is not progressive. Elevations in AST and bilirubin occur occasionally. In two patients (0.1% of total patients) who participated in clinical trials, cholestatic jaundice associated with elevations of serum aminotransferase levels occurred. The jaundice disappeared after ticlopidine was discontinued (3). Two cases of prolonged (12 to 15 weeks), severe cholestasis have been reported in a 91- and a 92-year-old (4,5). In an animal model of isolated perfused rat liver, repeated administration of ticlopidine induced cholestasis (6). The Canadian Adverse Drug Reaction Newsletter reported 11 cases of jaundice over 26 months; one patient died of hepatorenal syndrome (7). In all the reports the mean onset of jaundice from the start of the drug was 33 days (range 10 to 57) (4).

High titres of ANA have been reported in association with other drug-induced hepatitis, eg, hydralazine, methyl-dopa, isoniazid and sulphonamides (8,9). The mechanism of this phenomenon is unknown but likely immunological in origin.

**CONCLUSIONS**

Physicians prescribing ticlopidine hydrochloride should be aware that a potentially severe acute hepatitis associated with ANA positivity can occur. The drug should be discontinued if signs of liver dysfunction occur.

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References:
