tion, especially neuroretinitis, should alert the clinician to the possible diagnosis of cat-scratch disease.

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References

Hydroxyurea-Induced Hepatitis in Human Immunodeficiency Virus–Positive Patients

Recent reports suggest that hydroxyurea has potent antiretroviral effects when used in combination with nucleoside analogues [1]. The mechanism of action of hydroxyurea is inhibition of cytoplasmic ribonucleoside reductases. This inhibition reduces the intracellular pool of deoxyribonucleotides and enhances uptake of nucleoside analogues, such as zidovudine and didanosine [2]. We describe two cases of hepatic toxicity in HIV-positive patients being treated with hydroxyurea-containing regimens.

A 45-year-old woman was diagnosed with HIV infection in September 1986 (case 1). She did not drink alcohol or use illicit drugs. She had previously been treated with zidovudine, lamivudine, and saquinavir without the viral load becoming undetectable. In March 1998, her antiviral therapy was changed to nelfinavir, stavudine, didanosine, and hydroxyurea (500 mg b.i.d.). In June 1998, her antiviral therapy was changed to nelfinavir, stavudine, and saquinavir without the viral load becoming undetectable. In March 1998, her antiviral therapy was changed to nelfinavir, stavudine, didanosine, and hydroxyurea (500 mg b.i.d.). In June 1998, she developed severe abdominal pain, nausea, and vomiting.

Results of laboratory studies are shown in table 1. She had evidence of fulminant hepatitis with anion-gap metabolic acidosis. She died 18 hours after admission. At autopsy, she had severe hepatic necrosis, with no apparent cause.

A 42-year-old man was diagnosed with HIV infection in 1987 (case 2). He reported binge alcohol use. He was positive for antibody to hepatitis C virus with elevated transaminase levels. He had previously been treated with zidovudine, lamivudine, and saquinavir and later with indinavir, stavudine, and lamivudine. In May 1997, his therapy was didanosine, stavudine, ritonavir, and saquinavir. In March 1998, hydroxyurea (500 mg b.i.d.) was added to his treatment. In May 1998, he presented complaining of abdominal pain and nausea. Results of laboratory studies are shown in table 1.

His antiretroviral therapy was withheld, and his liver function gradually improved. In August 1998, treatment with didanosine, stavudine, saquinavir, ritonavir, and nevirapine without hydroxy-

Table 1. Results of laboratory studies for two HIV-positive patients with hydroxyurea-induced hepatitis.

<table>
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</thead>
<tbody>
<tr>
<td>CD4 cell count (/mm$^3$)</td>
<td>50</td>
<td>1,394</td>
<td>33</td>
<td>52</td>
<td>196</td>
<td>106</td>
<td>36</td>
</tr>
<tr>
<td>Aspartate aminotransferase level (0–45 U/L)*</td>
<td>31</td>
<td>1,245</td>
<td>43</td>
<td>43</td>
<td>197</td>
<td>128</td>
<td>22</td>
</tr>
<tr>
<td>Alanine aminotransferase level (3–36 U/L)</td>
<td>27</td>
<td>178</td>
<td>106</td>
<td>774</td>
<td>379</td>
<td>163</td>
<td></td>
</tr>
<tr>
<td>γ-Glutamyltransferase level (15–85 U/L)</td>
<td>0.3</td>
<td>20</td>
<td>0.5</td>
<td>0.6</td>
<td>3.8</td>
<td>0.9</td>
<td>0.5</td>
</tr>
<tr>
<td>Total bilirubin level (0.2–1.3 mg/dL)</td>
<td>0.3</td>
<td>20</td>
<td>76</td>
<td>116</td>
<td>166</td>
<td>135</td>
<td>74</td>
</tr>
<tr>
<td>Alkaline phosphatase level (3–125 U/L)</td>
<td>20</td>
<td>80</td>
<td>6</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>IgM antibody to hepatitis A virus</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibodies to hepatitis C virus</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B surface antigen</td>
<td>Negative</td>
<td>Positive</td>
<td></td>
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<tr>
<td>Hepatitis B surface antibody</td>
<td>Negative</td>
<td>Positive</td>
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</table>

* Values in parentheses are normal ranges.
urea was started. Results of his liver function tests have remained stable.

To our knowledge, this is the first report of hydroxyurea causing hepatic toxicity in HIV-positive patients. We found one previous report of hydroxyurea-induced hepatic toxicity in an HIV-negative patient who was receiving hydroxyurea for treatment of psoriasis [3]. Hepatitis occurred within days of the start of hydroxyurea therapy, resolved when hydroxyurea therapy was discontinued, and recurred when hydroxyurea was administered again. Other investigators have reported elevations in hepatocellular enzyme levels as a rare complication of hydroxyurea chemotherapy for cancer [4].

Nucleoside analogue reverse transcriptase inhibitors can cause lactic acidosis and hepatic failure resembling syndromes of mitochondrial dysfunction such as Reye’s syndrome [5, 6]. Nucleoside analogues inhibit both chromosomal DNA polymerases as well as mitochondrial DNA-pol-γ [6]. In fact, DNA-pol-γ is inhibited by much lower concentrations of nucleoside analogues than are chromosomal DNA polymerases [6]. Hydroxyurea may potentiate the mitochondrial toxicity of nucleoside analogues. Since hydroxyurea enhances the uptake of nucleoside analogues, mitochondrial poisoning by nucleoside analogues may be preferentially enhanced, leading to lactic acidosis and hepatic failure.

In case 2, the addition of hydroxyurea to therapy may have led to immune reactivation and a consequent transitory inflammatory response to hepatitis C virus–infected hepatocytes. Hydroxyurea suppresses retroviral replication, and some patients have an increase in lymphocyte function. Worsening of hepatitis C with antiviral therapy has been reported [7].

We have noted two hydroxyurea-associated cases of hepatocellular damage. The incidence of these complications is probably low, but prospective monitoring of hepatic function may be warranted for patients for whom antiviral regimens containing hydroxyurea have been started.

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References

Multidrug Resistance Among Streptococcus pneumoniae Isolated at a University Hospital in Eastern Tennessee

No local data from our institution have been prospectively collected and reported that examine antibiotic susceptibility among pneumococcal isolates. Because the newer-generation fluoroquinolones are now being used as treatment options for infections outside the CNS that are due to penicillin-resistant Streptococcus pneumoniae [1], we prospectively collected 50 clinical isolates for antibiotic susceptibility testing, which included β-lactam, macrolide, and fluoroquinolone antibiotics. Herein, we report the results of the local survey.

Fifty consecutive isolates of S. pneumoniae were collected between 27 August 1998 and 21 November 1998 at the University of Tennessee Medical Center at Knoxville. The medical center serves as a level 1 trauma center and tertiary care institution in eastern Tennessee. Only one isolate per patient was included in the survey, and an isolate from any specimen source was eligible for inclusion.

As per the performance standards of the National Committee for Clinical Laboratory Standards and specific zone diameter interpretive criteria [2], a 1-µg oxacillin disk was used to determine penicillin susceptibility. Isolates that were not susceptible (zone size, ≤19 mm) to oxacillin were further examined to determine penicillin, ceftriaxone, and erythromycin susceptibility by using the MicroScan MICROSTREP Panel (Dade International, West Sacramento, CA) as per the manufacturer’s instructions. Fluoroquinolone susceptibility testing was performed by using the Etest (AB BIODISK, Solna, Sweden). All procedures and interpretations of susceptibility categories were done according to the National Committee for Clinical Laboratory Standards [2].

A two-tailed Fisher’s exact test was used to statistically compare results of penicillin susceptibility testing for pneumococcal strains from three specimen sources: blood, respiratory tract, and ear. For the comparisons, differences at $P \leq .05$ were considered statistically significant.

The patients’ ages ranged from 9 months to 83 years; 34 patients (68%) were 18 years of age or older. Thirty-five patients (70%) were male.

Thirty-four (68%) of the isolates were from a respiratory source, and nine strains (18%) were recovered from blood cultures; the remaining seven strains were isolated from ear (six) and breast (one) specimens. Twenty-two (44%) of the 50 isolates were penicillin susceptible. The remaining isolates were either intermediately susceptible to penicillin or resistant.