Brief Communication: Severe Hepatotoxicity of Telithromycin: Three Case Reports and Literature Review

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Background: Telithromycin is a ketolide antibiotic approved by the U.S. Food and Drug Administration for acute bacterial infections causing sinusitis, bronchitis, and community-acquired pneumonia.

Objective: To describe 3 cases of severe hepatotoxicity in patients receiving telithromycin.

Design: Case reports.

Setting: A tertiary care medical center.

Patients: 3 previously healthy patients who had recently taken telithromycin and took no other prescription medications.

Measurements: Serologic, histologic, and liver function tests.

Results: Within a few days of receiving telithromycin, the patients presented with acute hepatitis. All had jaundice and markedly abnormal results on liver function tests. Results of viral serologic tests were negative. One patient spontaneously recovered, 1 required orthotopic liver transplantation, and 1 died. Histologic examination in the latter 2 patients showed massive hepatic necrosis.

Limitations: Two patients had some history of alcohol use. The frequency of severe telithromycin-related hepatotoxicity cannot be established with case reports.

Conclusions: Telithromycin can cause severe hepatotoxicity. Caution is advised in prescribing this drug pending additional postmarketing surveillance data.

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T elithromycin is the first ketolide antibacterial agent approved by the U.S. Food and Drug Administration (FDA). Derived from the macrolide class of antibacterial agents, telithromycin is approved for use in respiratory tract infections, including pneumonia, sinusitis, and bacterial exacerbations of chronic bronchitis (1). Ketolides are semisynthetic derivatives of the macrolides, with side-chain modifications on the 14-membered ring structure. These alterations substantially affect the molecule’s acid stability and create the ability to overcome most types of macrolide resistance (2). More than 30% of a telithromycin dose is metabolized by the liver; 50% is mediated by cytochrome P450 3A4, and 50% is cytochrome P450–independent (1). Approximately 20% of the dose is excreted unchanged in the bile, intestines, and urine (1).

We present 3 cases of drug-induced hepatotoxicity thought to be secondary to telithromycin. One case required liver transplantation, and 1 resulted in death. Each patient received medical care from at least 1 of the authors. Two of the 3 patients were hospitalized at Carolinas Medical Center in Charlotte, North Carolina, during the course of their treatment after taking telithromycin. All 3 cases have been reported to the FDA.

CASE REPORTS

Case 1

A 46-year-old white man with no clinically significant medical history presented with a 4-day history of dark urine, jaundice, and malaise. The patient had been in his usual state of health until he developed an ear and sinus infection. He was prescribed telithromycin. During the second day of therapy, he noticed malaise and a darkening of his urine; the next day, he developed slight jaundice and sought medical attention.

The patient reported fatigue, mild pruritus, a transient rash, and anorexia. He reported no toxin exposure, hepatic injury, or current or previous intravenous drug use. The patient reported taking no other prescription, herbal, or over-the-counter medications. He had no tattoos and did not drink alcohol.

On physical examination, the patient appeared tired but not chronically ill or in distress. His temperature was 36.8 °C, his vital signs were stable, and his lungs were clear. His abdomen was soft and nontender without hepatosplenomegaly. He had no outward signs of chronic liver disease.

The patient’s initial laboratory values were as follows: alanine aminotransferase level, 948 U/L (reference range, 0 to 40 U/L); aspartate aminotransferase level, 200 U/L (reference range, 0 to 40 U/L); alkaline phosphatase level, 291 U/L (reference range, 0 to 40 U/L); total bilirubin level, 65.0 μmol/L (3.8 mg/dL); direct bilirubin level, 40.5 μmol/L (2.37 mg/dL); and albumin level, 42 g/L (refer-
ence range, 35 to 55 g/L). On the basis of these values, telithromycin was withdrawn after 3 days of therapy. Results of serologic tests for hepatitis A, B, and C virus infection; mononucleosis; and HIV infection were all negative, as were results of tests for direct antinuclear antibodies and actin antibodies. The patient’s ceruloplasmin level was 230 mg/L, and his iron saturation was 31%.

After withdrawal of telithromycin, the patient began to feel better. In 2 weeks, his alanine aminotransferase level decreased to 450 U/L, accompanied by resolution of his jaundice. In 8 weeks, the patient’s alanine aminotransferase level had normalized.

Case 2

A 51-year-old white woman with no clinically significant medical history presented to her primary care physician with a 2-week history of cough and rhinorrhea. Because of persistent symptoms, she was placed on a 5-day course of telithromycin. When asked, the patient said that her only other medications were aspirin, 81 mg/d; a multivitamin; and vitamin E, 1000 IU/d, all of which she had been taking for a year. She developed icterus that week and was reevaluated by her physician. Laboratory studies at that time showed the following values: total bilirubin level, 162.5 μmol/L (9.5 mg/dL); alkaline phosphatase level, 188 U/L (reference range, 25 to 150 U/L); aspartate aminotransferase level, 930 U/L (reference range, 0 to 40 U/L); alanine aminotransferase level, 730 U/L (reference range, 0 to 40 U/L); γ-glutamyltransferase level, 250 U/L (reference range, 0 to 60 U/L); and direct bilirubin level, 57.3 μmol/L (3.35 mg/dL). No previous liver function tests had been done.

The patient was referred to a gastroenterologist. Additional questioning about her history revealed that she drank 2 glasses of wine per day. She did not smoke. Vital signs were stable, and an abdominal examination showed no hepatosplenomegaly, ascites, or tenderness. Findings on a neurologic examination were normal. Prothrombin time was 22.2 seconds (international normalized ratio, 2.51), amylase level was 64 U/L (reference range, 0 to 100 U/L), and lipase level was 414 U/L (reference range, 114 to 286 U/L). Results of tests for hepatitis A IgM antibody, hepatitis C antibody, and hepatitis B antigen were negative, as were the results of a test for antimitochondrial antibody. A test for anti-smooth-muscle antibody yielded weakly positive results, and a test for fluorescent antinuclear antibody yielded negative results. Abdominal ultrasonography showed a small echogenic liver with ascites and right pleural effusion. Portal vein flow was normal.

An ophthalmologic examination was performed and showed negative results for Kaiser–Fleischer rings. α1-Antitrypsin level was 0.93 g/L (reference range, 0.90 to 2.0 g/L) with MM phenotype. The patient underwent right-sided thoracentesis on 21 April 2005 secondary to moderate respiratory distress. Fluid analysis was consistent with a transudate, and cultures were negative.

One month later, the patient’s total bilirubin level had increased to 412.1 μmol/L (24.1 mg/dL) and her international normalized ratio had increased to 3.4. She was not encephalopathic. Computed tomography of the abdomen on 21 May 2005 showed a small liver with varices and splenomegaly. The patient was evaluated and listed for orthotopic liver transplantation. Subsequently, she was readmitted to the hospital with severe fatigue, muscle weakness, and continued jaundice. Her serum sodium level had decreased to 123 mmol/L (reference range, 134 to 143

The liver is only about one third of the normal size (480 g) and consists predominantly of diffuse collapse. Islands of surviving intact lobular parenchyma consist of regenerative nodules (arrows).
mmol/L). Her hyponatremia was corrected with administration of albumin and intravenous furosemide.

The patient underwent orthotopic liver transplantation. On entering the abdomen, the surgeon removed 1.5 L of clear ascitic fluid. The explanted liver weighed 480 g and appeared to have large areas of necrosis (Figure 1). The remainder of the abdominal exploration yielded normal findings. The patient was discharged 11 days after surgery. The histologic findings of the explanted liver were consistent with massive hepatic necrosis (Figure 2).

Case 3

A 26-year-old Hispanic man was admitted to the hospital after an 8-day history of jaundice, fever, melena, and hematemesis. Two weeks before admission, the patient had computed tomography of the sinuses that showed an enhancing lesion in the nasal cavity and nasopharynx on the left, possibly a neoplasm. The patient was prescribed and completed a course of telithromycin, 400 mg, 2 tablets once daily for 5 days. The patient and his wife reported that he drank eight 12-ounce beers every 2 weeks. He reported no long-term use of nonsteroidal anti-inflammatory drugs and no history of hepatitis, intravenous drug use, tattoos, or herbal medication use before admission.

On physical examination, the patient appeared severely ill and diaphoretic. His temperature was 35.6 °C, blood pressure was 123/67 mm Hg, pulse was 114 beats/min, respiratory rate was 20 to 40 breaths/min, and oxygen saturation was 100% on room air. The patient had jaundice and his abdomen was firm and tympanic, with notable hepatomegaly. There was notable tenderness to palpation in the mid-epigastric region and the right upper quadrant, with no rebound or guarding noted.

Initial laboratory tests showed a leukocyte count of 22 × 10⁹ cells/L, hemoglobin level of 128 g/L (reference range, 135 to 180 g/L), platelet count of 39 × 10⁹ cells/L (reference range, 150 to 450 × 10⁹ cells/L), blood urea nitrogen level of 5.0 mmol/L (30 mg/dL), creatinine concentration of 344.8 μmol/L (3.9 mg/dL), alkaline phosphatase level of 575 U/L (reference range, 39 to 117 U/L), aspartate aminotransferase level of 3638 U/L (reference range, 15 to 41 U/L), alanine aminotransferase level of

The figure shows total lobular necrosis, with pink hepatocytes lacking nuclei (area within arrows). Portal triads are densely infiltrated by lymphoid cells. (Hematoxylin–eosin; original magnification, ×10)
Telithromycin Hepatotoxicity

Table. Reported Hepatotoxicity in Head-to-Head Trials Involving Telithromycin*

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Comparator</th>
<th>Indication</th>
<th>Patients, n</th>
<th>Total Rate of Adverse Events in the Telithromycin Group versus the Comparator Group, %/%</th>
<th>Hepatic Adverse Events with Telithromycin versus the Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norrby et al., 2001 (12)</td>
<td>High-dose amoxicillin</td>
<td>CAP</td>
<td>395</td>
<td>35.4/35.2</td>
<td>0/1 Abnormal results on liver function tests; ALT level increased to 3 x ULN</td>
</tr>
<tr>
<td>Luterman et al., 2003 (10)</td>
<td>Amoxicillin–clavulanate</td>
<td>Sinusitis</td>
<td>754</td>
<td>42.2/46.9/42.9</td>
<td>NA No hepatic differences between groups</td>
</tr>
<tr>
<td>Quinn et al., 2003 (14)</td>
<td>Clarithromycin</td>
<td>Tonsillitis or pharyngitis</td>
<td>463</td>
<td>67.2/57.5 (P &lt; 0.05)</td>
<td>1/0 ALT, AST, and LDH levels increased 2.9, 7.6, and 2.5 x ULN, respectively</td>
</tr>
<tr>
<td>Buchanan et al., 2003 (9)</td>
<td>Cefuroxime</td>
<td>Sinusitis</td>
<td>593</td>
<td>36.1/31.4</td>
<td>NA No hepatic differences between groups</td>
</tr>
<tr>
<td>Pullman et al., 2003 (13)</td>
<td>Trovafloxacin</td>
<td>CAP</td>
<td>223</td>
<td>47.2/33.0 (P = 0.038)</td>
<td>5/0 Abnormal results on liver function tests; AST level increased to 3 x ULN</td>
</tr>
<tr>
<td>Zervos et al., 2003 (15)</td>
<td>Cefuroxime</td>
<td>Acute exacerbation of chronic bronchitis</td>
<td>373</td>
<td>30/32.3</td>
<td>1/0 ALT level increased to 3 x ULN</td>
</tr>
<tr>
<td>Mathers Dunbar et al., 2004 (11)</td>
<td>Clarithromycin</td>
<td>CAP</td>
<td>416</td>
<td>57/49</td>
<td>1/0 ALT level, 418 U/L; AST level, 295 U/L</td>
</tr>
<tr>
<td>Aubier et al., 2002 (16)</td>
<td>Amoxicillin–clavulanate</td>
<td>Acute exacerbation of chronic bronchitis</td>
<td>325</td>
<td>23.8/36.9 (P = 0.015)</td>
<td>NA No laboratory safety differences between groups</td>
</tr>
<tr>
<td>Ferguson et al., 2004 (17)</td>
<td>Moxifloxacin</td>
<td>Sinusitis</td>
<td>349</td>
<td>34.7/27.8</td>
<td>NA No hepatic differences between groups</td>
</tr>
<tr>
<td>Tellier et al., 2004 (18)</td>
<td>Clarithromycin</td>
<td>CAP</td>
<td>575</td>
<td>44.6/44.9</td>
<td>10/7 Elevated levels of ALT and AST</td>
</tr>
</tbody>
</table>

**ALT = alanine aminotransferase; AST = aspartate aminotransferase; CAP = community-acquired pneumonia; LDH = lactate dehydrogenase; NA = not available; ULN = upper limit of normal.

† This study involved 2 telithromycin groups, one that received the drug for 5 days and another that received the drug for 10 days. The first 2 values given are for these 2 groups, respectively.

2200 U/L (reference range, 17 to 63 U/L), and total bilirubin level of 233 μmol/L (13.6 mg/dL) (reference range, 7 to 34 μmol/L [0.4 to 2.0 mg/dL]). The prothrombin time was 25.7 seconds (reference range, 11.1 to 13.5 seconds), partial thromboplastin time was 38 seconds (reference range, 20 to 34 seconds), and international normalized ratio was 2.3. Abdominal radiography showed no high-grade obstruction or gross pneumoperitoneum. Computed tomography without contrast of the abdomen and pelvis showed moderate ascites and bowel-wall thickening.

Acetylcysteine therapy was initiated, but levels of acetylaminophen, salicylate, and ethylene glycol were subsequently found to be normal. The patient had upper endoscopy, which showed only gastritis. During the procedure, the patient became hypotensive and developed cardiopulmonary failure requiring resuscitation. General surgeons were consulted for possible abdominal catastrophe and performed a deep peritoneal lavage with removal of nonbloody ascitic fluid.

On the second hospital day, the patient required pressors and continued ventilator support. He had metabolic acidosis despite bicarbonate infusion. Dialysis was begun but did not correct his acidic state. Results of all serologic tests—including tests for HIV infection; Epstein–Barr virus infection; hepatitis A, B, and C virus infection; antinuclear antibody; and leptospirosis antigen—were negative.

On day 3, despite aggressive therapy, the patient was hypotensive and had continued refractory acidosis; his respiratory status worsened. Despite receiving fluid resuscitation and pressors, the patient became asystolic and died. The autopsy showed hepatomegaly; liver weight was 2850 g, and massive hepatic necrosis with lymphocytic inflammatory response characteristic of hypersensitivity reaction was noted (Figure 3).

**DISCUSSION**

According to the World Health Organization, an adverse drug reaction is defined as a noxious, unintended response to a drug that occurs at doses normally used in humans for prophylaxis, diagnosis, or therapy or for modification of physiologic function (3). Drug-induced liver injury is a common form of adverse drug reaction and
accounts for more than 50% of cases of acute liver failure in the United States (4). Although most of these cases are due to acetaminophen overdose, it is estimated that 13% are secondary to idiosyncratic drug reactions and that most are due to host-dependent factors (5, 6). These reactions can be characterized as hepatocellular, cholestatic, or mixed, according to clinical or histologic criteria (7). Unexpected, idiosyncratic reactions are the most dangerous; more than 75% result in liver transplantation or death (4).

In any suspected case of drug-induced liver injury, other potential causes must be carefully excluded by serologic and radiologic evaluation. Each of our patients presented with acute hepatitis shortly after receiving a course of telithromycin. Two of the 3 patients had some history of alcohol use; however, there was no history of liver dysfunction and no histologic evidence of alcohol-induced liver injury. Histologic examination in 2 of the 3 patients showed massive hepatic necrosis, consistent with drug-induced injury. No other drugs were involved, and other potential causes of injury were excluded. On a scale based on 10 questions for estimating the probability of an adverse drug reaction (8), all 3 cases were determined “probable” (total scores of 6 for case 1, 6 for case 2, and 5 for case 3). Withdrawal of telithromycin led to clinical improvement in only 1 of the 3 cases.

To identify historical instances of hepatotoxicity with telithromycin, we searched for relevant English-language publications in MEDLINE from 1966 to November 2005, reviewed prescribing information and the FDA’s Adverse Event Reporting System from April 2004 through June 2005, and requested pertinent data on file at Sanofi-Aventis (Paris, France). We found 11 publications that reported telithromycin’s comparative efficacy and tolerability (2, 9–18). Clinical and bacteriologic cure rates were similar to those of comparators in all instances. Total adverse event rates were similar between telithromycin and comparators in 8 trials (Table) (2, 9–12, 15, 17, 18). However, total adverse event rates were statistically significantly higher in the telithromycin arms of 2 trials in which trovafloxacin (13) and clarithromycin (14) were used as comparators and were statistically significantly lower in the telithromycin arm in 1 trial (16) in which amoxicillin–clavulanate was used as the comparator. More specific to this discussion are the reported rates of hepatic adverse events, which were minimal (<5%) in all trials (Table) but were more common in the telithromycin group in 6 trials (2, 11, 13–15, 18). None of the trials reported long-term hepatic side effects or hepatic deaths. History or presence of hepatic impairment or illness was an exclusion criterion for 9 of the clinical trials (2, 9–16).

Data from telithromycin’s prescribing information (1) state that abnormal results on liver function tests (alanine aminotransferase levels ≥3 times the upper limit of normal) occurred in 1.6% of patients receiving telithromycin and 1.7% of those receiving the comparator drug and that reversible hepatitis, with or without jaundice, occurred in 0.07% of patients receiving telithromycin. Similar reports of infrequent severe hepatic dysfunction and liver failure resulting in death appear in the prescribing information for both of the macrolides, azithromycin (19) and clarithromycin (20). The prescribing information for telithromycin advises caution in patients with a history of hepatitis or jaundice associated with this drug.

Phase III data provided by Sanofi-Aventis described 7 cases of hepatitis or hepatocellular damage in patients taking telithromycin (Sanofi-Aventis. Personal communication. 1 July 2005). Alcohol use, baseline elevations in aminotransferase levels, and hepatitis B virus infection were confounders in 4 of the cases. All but 1 case (recurrent hepatitis without reexposure to telithromycin) resolved without sequelae. Sanofi-Aventis also reported that 3 cases in a large study comparing telithromycin with amoxicillin-clavulanate met safety end points for possible substantial drug-related hepatic injury. Two of these cases were determined to have a compatible temporal relationship between the hepatic adverse event and telithromycin exposure and the third was determined to involve medical complications, but an effect of the drug could not be discounted. Postmarketing surveillance has also produced reports of infrequent hepatocellular or cholestatic hepatitis with and without jaundice.

The FDA’s Adverse Event Reporting System (21) describes 10 postmarketing cases of hepatic adverse events associated with telithromycin use. Eight of these cases involve a wide range of additional agents taken concomitantly with telithromycin. Severity of reactions ranged from serious to fatal (2 patients died) and involved cholestatic hepatitis, abnormal aminotransferase levels, increased bilirubin levels, liver disorder, cholestatic jaundice, and hepatocellular damage. Duration of telithromycin use ranged from 1 to 30 days, and patient ages ranged from 35 to 85 years. Only 2 cases were described with telithromycin in the absence of other agents; both involved increased aminotransferase levels and required hospitalization, but neither resulted in death.

Also noteworthy are interactions with other drugs that may theoretically potentiate hepatotoxicity when used concomitantly with telithromycin. Simvastatin levels can increase substantially when the drug is coadministered with telithromycin (1). Hepatitis has been documented when simvastatin is used with another agent known to increase simvastatin levels (22). When telithromycin is coadministered with ketoconazole or itraconazole, telithromycin levels can in-
drug pending further postmarketing surveillance data. The relationship between telithromycin and alcohol use warrants further study.

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Grant Support: None.

Potential Financial Conflicts of Interest: None disclosed.

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