Severe Hepatotoxicity of Telithromycin

TO THE EDITOR: Although Clay and colleagues’ article on possible telithromycin-induced hepatic toxicity was of interest (1), some clarifications are needed. In case 1, the authors report that the patient presented with a 4-day history of dark urine, jaundice, and malaise that began on the second day of telithromycin therapy. However, the authors then state that the drug was “withdrawn after 3 days of therapy” when laboratory results (presumably obtained at the time of patient presentation) were obtained. The time course is confusing as reported.

In case 3, the authors note that “levels of acetaminophen, salicylate, and ethylene glycol were subsequently found to be normal.” Generally, there are no “normal” concentrations of acetaminophen and salicylate (unless the patient was taking these medications, in which case “normal ranges” may be appropriate). However, the case report did not suggest that the patient was taking either of these medications. Although suggestions about treatment of ethylene glycol ingestion recommend monitoring serum concentrations (along with a host of other things), ethylene glycol is generally not found in the body unless there has been an exposure (deliberate or accidental) (2). This also needs clarification for readers.

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Potential Financial Conflicts of Interest: None disclosed.

References

IN RESPONSE: In case 1, the patient started to notice dark urine on day 2 of treatment with telithromycin. When his wife noted continued symptoms on day 3, the patient decided to stop taking the medication. It was a week later, when the patient presented to his physician, that the laboratory tests were performed and abnormalities were noted.

With respect to case 3, I would say that the levels of acetaminophen, salicylate, and ethylene glycol were negative, which was expected based on the history given by the patient.

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Potential Financial Conflicts of Interest: None disclosed.

Preventing Scientific Fraud

TO THE EDITOR: Recent discussions of research misconduct (1, 2) highlight a continuing problem. Being a medical scientist does not make a person immune to human frailties. Indeed, far worse crimes have been committed by doctors (3). Medical publishers also have their frailties, perhaps striving too hard to publish medical investigations with the greatest impact or controversy. This may inadvertently encourage fraud. While accepting that institutions play their role to ensure the integrity of research conducted under their umbrella, journals and journal editors too must accept responsibility to ensure truthful reporting of results. Paying subscribers and nonpaying readers deserve quality assurance measures in this regard. This requires time, effort, and resources for journals and their peer-review processes. Given the importance to patients and health care providers of employing best practice, greater acknowledgment of those already contributing to peer review and quality assurance is warranted. However, even greater scrutiny of research data is required. This could and should be provided by journals. For a minimum modest fee, of say $10 per author of papers accepted for publication, further checks could be made to a proportion of articles. Sponsored studies might attract a higher fee for journal publication. This could be invested to promote quality assurance. For example, 1 paper in 20 might receive additional scrutiny and 1 in 200 might receive extensive scrutiny of all relevant data.

The real possibility of misconduct being identified coupled with the imposition of adequate sanctions would be a powerful disincentive. Surely patients and health care providers deserve no less.

Prevention is better than retraction.

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Potential Financial Conflicts of Interest: None disclosed.

References

TO THE EDITOR: The recent article about the importance of integrating retraction notices with their original reports (1) noted their treatment in PubMed but not the procedures followed in the Science Citation Index (SCI), the electronic version of which is included in the Web of Science.

Ever since the SCI was launched in the 1960s, it has indexed published retractions. In each case, a citation link was established between the retraction, that is, “correction,” and the original source article. To find retractions, like all other corrections, all one had to do was conduct a cited reference search based on the author, journal, and year of publication of the retracted paper. This would yield a list of all items that cited the original work, including the retractions, which, like all other corrections, would be coded as such. However, in 1996, the SCI amplified its treatment of retractions by including
the notation for the retraction together with the bibliographic citation for the source item. If one does a search on a subject or an author and finds a paper that has been retracted, the retraction can be seen immediately adjacent to the source entry. Thus, for example, the entry for W.S. Hwang’s 2005 paper in Science on patient-specific embryonic stem cells is followed by SCIENCE 311 (5759): 335-335 JAN 20 2006, the imprint data for the retraction. When one conducts a cited reference search on the original paper (Hwang HS, Science, 2005), one immediately sees the statement, “This article was retracted see Science 311, 335, Jan. 20, 2006.”

In previous generations, authors often unwittingly cited retracted research because they did not or could not check citation indexes. Today, there is no excuse because access to PubMed and Web of Science is widely available.

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Potential Financial Conflicts of Interest: All of the authors are connected to the purveyor of the Science Citation Index and Web of Science.

Reference

TO THE EDITOR: We read the article on research misconduct and the Poehlman case (1) with great interest. Eric Poehlman was hired by the University of Montréal and obtained a senior Canadian Chair position from the Canadian Institutes of Health Research in 2002. He held a professorship position in the department of nutrition at our university and was dismissed when we learned of his misconduct at the University of Vermont. The news of Dr. Poehlman’s scientific fraud was a devastating blow to all Canadian scientists and students who worked with him. The possibility that scientific misconduct by Dr. Poehlman had continued at our institution prompted us to perform a full review of all data from projects funded by the Canadian Institutes of Health Research that were collected under his supervision. This included the verification of all electronically stored data as well as raw data from subjects’ records. All student and research assistants testified that no data entry had ever been purposefully altered. In addition, the results of one study funded by a private company were audited by an independent external committee that found no evidence of fraud. This evidence convinced the research committee of our university to allow us to continue Dr. Poehlman’s projects after his dismissal and the Canadian Institutes of Health Research to resume funding of all projects. We are therefore confident that the data reported in the 6 scientific papers published by Dr. Poehlman while working at our institution (2–7) are untainted. Per our university standard requirements, all raw data are available for examination 5 years after publication.

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Potential Financial Conflicts of Interest: None disclosed.

References

IN RESPONSE: Dr. Noble feels that journals should do more to prevent scientific fraud. He proposes that journals do an in-depth investigation of randomly chosen articles. Research misconduct is almost always detected inside the institution. In 1988, Dr. Rennie proposed doing such a random audit of accepted manuscripts as an experiment, the results to be published only in aggregate (1, 2). The idea was to measure the frequency of the grossest forms of misconduct, for example, how often researchers sent in papers based entirely on fabricated patients, as had happened in the cases of Soman and of Darsce (3). Dr. Rennie proposed that acceptance for publication would be conditional on the authors allowing the auditors full access to their places of work.

The problem with making such a proposal routine is that editors would face insuperable barriers in access to research institutions and have no power or expertise (nor time or money) to carry out adequate investigations. In addition, the pretest probability of outand-out fraud is doubtless very low. Editors’ lack of forensic skills would guarantee that routinely testing for fraud would have a low sensitivity (4), so the probability of detecting fraud would be extremely low, and we would miss many cases. Moreover, the scheme would have costs, starting with Dr. Noble’s proposed fee and the random selection of a target, which would undoubtedly create an atmosphere of distrust. In the end, we agree with Kennedy (5) that routinely auditing a random selection of all papers is a bad plan.

In fact, most journals investigate the validity of articles that they intend to publish. Both the Journal of the American Medical Association and Annals of Internal Medicine do a detailed evaluation of the
statistical methods and often ask for the study protocol. However, we see no workable alternative to starting with the assumption that authors are trying to offer a faithful depiction of the facts. We see our main mission as presenting research reports in a form that makes it easy for scientific peers to evaluate them and try to reproduce the findings, which is the best, and certainly the most practical, way to detect results that are wrong for whatever reason. The true test of any discovery begins with publication.

We thank Dr. Garfield and his colleagues for reminding all of us that the SCI is another way to find articles that have been retracted. We agree that present-day authors have no excuse for citing a retracted article. Still, they do.

Dr. Garrel and her colleagues have informed the research community that their university has investigated the 6 articles written by Dr. Poehlman during his tenure at the University of Montréal. The university has fulfilled its obligation, and we have fulfilled ours by publishing its findings. May all universities and journals take their responsibilities so seriously.

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Potential Financial Conflicts of Interest: None disclosed.

References

CLINICAL OBSERVATIONS

Symptomatic Myopathy due to Red Yeast Rice

Background: Red yeast rice is a dietary supplement that contains 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors and is used for self-treatment of hyperlipidemia.

Objective: To report a case of symptomatic myopathy associated with use of red yeast rice.

Case Report: In January 2005, a 61-year-old woman presented for a general health assessment. She reported a history of hyperlipidemia but had no symptoms at rest or with activities. Her medications included an estradiol transdermal patch (0.05 mg/wk), aspirin (81 mg/d), and a multivitamin (once daily). Her vital signs were normal, weight was 70.9 kg, and body mass index was 29.2 kg/m². Results of thyroid, chest, heart, abdomen, vascular, musculoskeletal, and neurologic examinations were normal. Laboratory studies showed hyperlipidemia (Table), for which the hepatic HMG-CoA reductase inhibitor simvastatin (20 mg/d) was started.

At a follow-up examination in April 2005, the patient reported no symptoms, and laboratory studies showed improved lipid levels and no evidence of hepatopathy or myopathy. The daily dose of simvastatin was increased to 40 mg. In May 2005, severe and diffuse myalgias developed. Laboratory studies showed markedly elevated serum levels of the muscle enzyme creatine kinase. The simvastatin

<table>
<thead>
<tr>
<th>Date of Evaluation</th>
<th>Symptoms</th>
<th>Creatine Kinase Level, U/L</th>
<th>Total Cholesterol Level, mmol/L (mg/dL)</th>
<th>Triglyceride Level, mmol/L (mg/dL)</th>
<th>HDL Cholesterol Level, mmol/L (mg/dL)</th>
<th>LDL Cholesterol Level, mmol/L (mg/dL)</th>
<th>AST Level, U/L</th>
<th>Medication Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 January 2005</td>
<td>None</td>
<td>ND</td>
<td>8.02 (310)</td>
<td>1.45 (128)</td>
<td>2.22 (86)</td>
<td>5.12 (198)</td>
<td>32</td>
<td>Began simvastatin, 20 mg/d</td>
</tr>
<tr>
<td>13 April 2005</td>
<td>None</td>
<td>189</td>
<td>6.47 (250)</td>
<td>2.29 (203)</td>
<td>1.71 (66)</td>
<td>3.70 (143)</td>
<td>27</td>
<td>Daily dose of simvastatin increased to 40 mg</td>
</tr>
<tr>
<td>6 May 2005</td>
<td>Diffuse myalgias</td>
<td>451</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>34</td>
<td>Simvastatin withdrawn</td>
</tr>
<tr>
<td>11 June 2005</td>
<td>None</td>
<td>170</td>
<td>6.80 (263)</td>
<td>1.41 (129)</td>
<td>1.86 (72)</td>
<td>4.29 (166)</td>
<td>30</td>
<td>Began red yeast rice preparation, 600 mg 2 times per day</td>
</tr>
<tr>
<td>9 September 2005</td>
<td>Diffuse myalgias</td>
<td>475</td>
<td>5.77 (223)</td>
<td>2.00 (177)</td>
<td>1.89 (73)</td>
<td>2.97 (115)</td>
<td>ND</td>
<td>Red yeast rice withdrawn</td>
</tr>
<tr>
<td>10 October 2005</td>
<td>None</td>
<td>122</td>
<td>6.26 (242)</td>
<td>1.60 (142)</td>
<td>1.60 (62)</td>
<td>3.93 (152)</td>
<td>ND</td>
<td>None</td>
</tr>
</tbody>
</table>

* Reference ranges were 38–176 U/L and 12–31 U/L for creatine kinase and AST levels, respectively. Desirable values for total cholesterol were <5.17 mmol/L (<200 mg/dL), normal values for triglycerides were <1.69 mmol/L (<150 mg/dL), desirable values for HDL cholesterol level were >1.55 mmol/L (>60 mg/dL), and optimal values for LDL cholesterol level were <2.59 mmol/L (<100 mg/dL). AST = aspartate aminotransferase; HDL = high-density lipoprotein; LDL = low-density lipoprotein; ND = not done.
was withdrawn, symptoms resolved, and laboratory studies repeated in July 2005 showed a normal serum creatine kinase level.

Instead of simvastatin, the hyperlipidemia was treated with a rigorous program of dietary restrictions, weight loss, and exercise. Shortly after beginning this regimen, the patient decided to begin taking the over-the-counter herbal preparation red yeast rice (rice that has been fermented by the red yeast Monascus purpureus) for her hyperlipidemia. In September 2005, severe and diffuse myalgias recurred. Again, laboratory studies showed a markedly elevated serum creatine kinase concentration. Thyroid-stimulating hormone level and erythrocyte sedimentation rate were normal. The red yeast rice was withdrawn, and the patient’s symptoms resolved. Follow-up laboratory studies in October 2005 showed a normal serum creatine kinase level. The hyperlipidemia is now being treated with dietary restrictions, weight loss, and exercise.

Discussion: Red yeast rice has been used as a food preservative and medicine in China since the year 800 (1). The main active antihyperlipidemic ingredients in red yeast rice are HMG-CoA reductase inhibitors, including lovastatin (2). Compared with placebo, red yeast rice substantially decreases total cholesterol, low-density lipoprotein, and triglyceride levels (1).

Myopathy is a well-known complication of HMG-CoA reductase inhibitors. Because red yeast rice contains HMG-CoA reductase inhibitors, it too may cause myopathy, as implicated in several case reports (3, 4). One case occurred in a renal allograft recipient, a 28-year-old woman, who developed asymptomatic elevation of serum creatine kinase levels after ingestion of red yeast rice, garlic (Allium sativum), and danshen root (Salvia miltiorrhiza) (3). The creatine kinase elevation resolved after withdrawal of all herbal preparations. Of note, she was also taking cyclosporine, which can interfere with the metabolism of HMG-CoA reductase inhibitors. Another case involved a 50-year-old man who developed diffuse myalgias after taking red yeast rice and ginseng (4). He was found to have an elevated serum creatine kinase level. After the red yeast rice and ginseng were withdrawn, his symptoms and serum creatine kinase elevation resolved. Although ginseng has not been reported to cause myopathy in humans, it can cause myopathy in guinea pigs.

The present report describes the case of a woman who developed symptomatic myopathy after taking the HMG-CoA reductase inhibitor simvastatin and after consuming red yeast rice. In both instances, her diffuse myalgias and elevated serum creatine kinase level resolved after the substance was withdrawn. These findings suggest that, like any HMG-CoA reductase inhibitor, red yeast rice can cause myopathy. Given the widespread use of over-the-counter herbal preparations (5), clinicians should be aware of this important potential adverse reaction.

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Potential Financial Conflicts of Interest: None disclosed.

References

Correction
Correction: Trials That Matter: Should We Routinely Measure Homocysteine Levels and “Treat” Mild Hyperhomocysteinemia?

In an editorial on routine measurement of homocysteine levels (1), the Potential Financial Conflicts of Interest section should have read as follows: Grants received: I.H. Rosenberg (National Institutes of Health).

Reference