Ramipril-Induced Liver Injury: Case Report and Review of the Literature

Antonios Douros, Wolfgang Kauffmann, Elisabeth Bronder, Andreas Klimpel, Edeltraut Garbe, and Reinhold Kreutz

BACKGROUND
Ramipril, an inhibitor of the angiotensin-converting enzyme (ACEI), is a drug commonly used in the therapy of hypertension. ACEI-induced hepatotoxicity is rare, and most of the reported cases are associated with captopril. Here, we present the first case of ramipril-induced liver injury proven by positive rechallenge and a review of the literature including the data from the US Food and Drug Administration adverse event reporting system (FAERS).

METHODS
Patient data were collected in the Berlin Case-Control Surveillance Study for adverse drug reactions. PubMed research on ACEI-induced hepatotoxicity included all ACEIs except captopril; analysis of the FAERS database focused on ramipril-induced hepatotoxicity in the period 2009–2011.

RESULTS
A 40-year-old male patient presented with acute onset jaundice and highly (>20-fold increase of alanine aminotransferase (ALT)) elevated liver enzymes (LEs). Viral or autoimmune hepatitis and biliary etiology were ruled out. Withdrawal of several medications including ramipril resulted in an immediate decrease in LEs, whereas a subsequent re-exposure with ramipril resulted in a striking increase in LEs (>35-fold increase of ALT). After definitely discontinuing ramipril, a rapid decline in LEs was observed, suggesting a certain causal relationship between drug intake and hepatic damage. Analysis of the FAERS database retrieved 65 cases of ramipril-associated hepatotoxicity, with jaundice being the most frequent hepatic adverse event. PubMed research detected 23 relevant publications, with enalapril being the ACEI most commonly reported as being associated with liver injury.

CONCLUSIONS
ACEI-induced hepatotoxicity is rare. Our case confirms a hepatotoxic potential of ramipril, highlighting the need for alertness among physicians regarding this matter.

Keywords: blood pressure; drug-induced liver injury; hypertension; ramipril.

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review of the literature on ACEI-induced hepatotoxicity was performed. Captopril was thereby excluded, as captopril-induced hepatotoxicity represents a well-established disease entity. Furthermore, we performed a search in the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) on ramipril-associated hepatic adverse events.

METHODS

Patient data for adverse drug reactions were collected in the Berlin Case-Control Surveillance Study (FAKOS), which was conducted from 2000 until 2011 to study serious toxicity of drugs. Details of this program have been previously reported. Literature research in PubMed included the following terms: “ACE inhibitor and hepatotoxicity,” “ACE inhibitor-induced liver injury,” “ACE inhibitor-induced hepatic damage,” “ACE inhibitor and jaundice,” and “ACE inhibitor and hepatic failure.” Articles published in languages other than English were not considered. Cases concerning captopril were excluded because captopril-induced hepatotoxicity has been thoroughly reviewed in the past.

Our analysis of the FAERS database was for the period between the first quarter of 2009 and the last quarter of 2011. The first search criteria were the names of ramipril-containing drugs: “ramipril,” “altace,” “delix,” “vesdil,” “prilace,” and “triacet.” We used the drugs labeled “primary suspect”; drugs specified as “secondary suspect” or “concomitant” were not considered in our analysis. Reports containing the following terms were analyzed: “hepatic failure,” “acute hepatic failure,” “hepatitis,” “hepatitis acute,” “hepatitis fulminant,” “hepatic function abnormal,” “hepatic encephalopathy,” “hepatotoxicity,” “cholestatic hepatitis,” “cholestasis,” “hepatic steatosis,” “hepatic enzyme increased,” “hepatic necrosis,” “cholelithiasis,” “hepatic lesion,” “liver disorder,” “liver injury,” “jaundice,” “hepatic injury,” “cholestatic liver injury,” and “jaundice cholestatic.” Multiple reports of the same adverse event were identified and consolidated by linking the Individual Safety Report code, unique for every single case of adverse event.

We determined the type of DILI in the cases retrieved using the ratio of the relative rise of alanine aminotransferase (ALT), as a multiple of its upper limit of normal, to the relative rise of alkaline phosphatase (ALP), as proposed by Benichou et al. Cholestatic DILI had a ratio <2, mixed DILI had a ratio of 2–5, and hepatocellular DILI had a ratio >5. When the respective values were missing, liver histology was taken into consideration. When laboratory values and liver biopsy were lacking, cases were graded as unclassifiable.

RESULTS

Case report

A 40-year-old white male patient was admitted to hospital with a 5-day history of jaundice. He had a long history of arterial hypertension and diabetes mellitus secondary to alcohol-induced chronic pancreatitis. During the last acute attack of his chronic pancreatitis three months prior, the patient had shown increased ALT values (354 U/L on discharge day). Two days before admission, a blood sample was collected from a general practitioner and showed a value of 888 U/L, which represented a 20-fold elevation over the upper limit of normal of ALT; the ALP was also markedly elevated to 599 U/L, representing an almost 5-fold elevation over the upper limit of normal. Bilirubin was slightly increased as well (32.5 µmol/L).

On admission day, the patient denied any pain or fever. He had been drinking approximately 1 L of beer per day for the last 5 years. His medication included omeprazole (40 mg/d), simvastatin (80 mg/d), insulin detemir (long-acting insulin analogue), and insulin lispro (fast-acting insulin analogue). Furthermore, the patient reported having discontinued his ramipril medication (10 mg/d) 4 days ago after reading the package insert, which listed liver damage and jaundice as possible adverse effects. He had been receiving ramipril uneventful for the last 10 months. Blood test on admission day showed a decrease in ALT (317 U/L), ALP (364 U/L), and bilirubin (11.1 µmol/L) values. Serologic testing for hepatitis A, B, or C as well as several autoantibodies tests (antinuclear antibodies, antimitochondrial antibodies, liver-kidney microsomal type 1 antibodies, antisoluble liver antigen antibodies, c-anti-neutrophil cytoplasmic antibodies, p-anti-neutrophil cytoplasmic antibodies, antiliver cell membrane antibodies, and antiliver cytosolic antigen type 1 antibodies) were all negative. A biliary cause was ruled out by abdominal sonography. Liver biopsy showed parenchymal damage and inflammation with no signs of steatosis.

All medications except for insulin were immediately withdrawn. On hospital day 2, another blood test showed a further decrease in ALT (242 U/L). On the same day, ramipril therapy was reinitiated (10 mg/d). After re-exposure with ramipril, a striking elevation of liver enzymes was observed (hospital day 6: ALT = 1555 U/L; ALP = 523 U/L). Bilirubin was only marginally increased (23.1 µmol/L). Consequently, ramipril was definitely discontinued. This discontinuation resulted in a rapid decline of the respective laboratory values (hospital day 11: ALT = 322 U/L; ALP = 276 U/L; bilirubin = 11.8 µmol/L). On hospital day 11, the patient was discharged in good condition, with insulin being his only medication.

Figure 1 illustrates the time course of the rise of the 2 liver enzymes.

Literature research

Table 1 shows the 23 relevant publications that were retrieved by our analysis of the PubMed database. Enalapril was the ACEI most commonly reported associated with DILI. Mean age of patients was 55.1 ± 16.3 years. The time interval between initiation of the respective medication and onset of symptoms or documentation of abnormal values of liver enzymes varied from 3 days to 4 years. The most frequent symptoms were jaundice (68%) and pruritus (28%). Thirteen DILIs showed a cholestatic pattern of hepatic damage, 6 cases showed a hepatocellular pattern, 4 cases showed a mixed pattern, and 2 cases remained unclassifiable. Cholestatic liver injury was the most common pattern associated with all ACEIs apart from lisinopril, for which
hepatocellular liver injury was found in all 5 cases. In 1 case, a re-exposure with the responsible medication occurred (enalapril), which led to a new elevation of liver enzymes. Concerning clinical outcome, 18 patients showed a clinical improvement with normalization of the respective laboratory values, 3 patients developed chronic liver disease, and 4 patients died.

FDA research

Table 2 illustrates the results of our search in the FAERS database for the years 2009–2011. Our analysis retrieved 88 single adverse event reports of ramipril-associated hepatotoxicity corresponding to 65 single case subjects. Of those, 53 case subjects had only 1 hepatic adverse event reported, whereas 12 case subjects had >1. The FAKOS case described above was not included in the FAERS database. The most frequent hepatic adverse events associated with ramipril were jaundice (25%) and elevated liver enzymes (22%).

DISCUSSION

In 2000, the Heart Outcomes Prevention Evaluation Study showed a reduced cardiovascular mortality in high-risk patients after daily treatment with 10 mg ramipril.4 This important finding has subsequently led to high prescription rates of this ACEI worldwide.15 Ramipril is a well-tolerated drug and has been mainly associated with mild adverse effects such as cough. Although hepatic adverse effects ranging from hepatitis to hepatic failure are mentioned in the prescribing information,16 only 3 cases of ramipril-associated DILI have been published so far.11 All of them lacked re-exposure and thus certain causality. Here, we present the first report of a ramipril-induced liver injury proven by positive rechallenge.

Our patient had a history of chronic pancreatitis on the grounds of alcohol abuse, implicating an alcoholic etiology of liver injury. However, liver biopsy demonstrated DILI and importantly no typical features of alcohol-induced liver damage—for example, no signs of hepatic steatosis. Several other differential diagnoses were excluded by serology and abdominal sonography. Furthermore, DILI was considered as a potential cause of the initial event of liver injury in the patient, and all medications were therefore discontinued. No formal separate and systematic rechallenge testing with the originally applied drugs was subsequently planned. Nevertheless, ramipril was readministered by the treating physician in agreement with the patient because it appeared effective to control his hypertension and it was considered as a less-likely candidate responsible for the observed liver injury. However, re-exposure to ramipril led to a new elevation of liver enzymes (“positive rechallenge”), fulfilling thus all requirements for a certain drug causality according to WHO criteria.12 Consequently, no further rechallenge testing with simvastatin or omeprazole as other potentially hepatotoxic drugs that were originally taken by the patient was considered.

We also applied the Roussel Uclaf Causality Assessment
Table 1. Cases of angiotensin-converting enzyme inhibitor–induced liver injury reported in the English medical literature according to PubMed search (cases of captopril-induced liver injury excluded; n = 25)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Age, y</th>
<th>Sex</th>
<th>Time to onset</th>
<th>Symptoms</th>
<th>Pattern of liver injury</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enalapril</td>
<td>34</td>
<td>Male</td>
<td>10 days</td>
<td>Asymptomatic</td>
<td>Cholestatic</td>
<td>Normalization</td>
<td>Shionoiri et al. 20</td>
</tr>
<tr>
<td>Enalapril</td>
<td>54</td>
<td>Female</td>
<td>7 weeks</td>
<td>Asymptomatic</td>
<td>Mixed</td>
<td>Normalization</td>
<td>Rosellini et al. 21</td>
</tr>
<tr>
<td>Enalapril</td>
<td>67</td>
<td>Female</td>
<td>6 weeks</td>
<td>Jaundice, pruritus</td>
<td>Cholestatic&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Normalization</td>
<td>Todd et al. 22</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>55</td>
<td>Male</td>
<td>2 weeks</td>
<td>Jaundice, fever, myalgia, hepatic encephalopathy</td>
<td>Hepatocellular&lt;sup&gt;2&lt;/sup&gt;</td>
<td>ALF, death</td>
<td>Larrey et al. 23</td>
</tr>
<tr>
<td>Enalapril</td>
<td>59</td>
<td>Female</td>
<td>2 months</td>
<td>Asymptomatic</td>
<td>Unclassifiable&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Normalization</td>
<td>Kitai et al. 24</td>
</tr>
<tr>
<td>Enalapril</td>
<td>51</td>
<td>Male</td>
<td>1 month</td>
<td>Jaundice, confusion</td>
<td>Cholestatic</td>
<td>Normalization</td>
<td>Hagley et al. 25</td>
</tr>
<tr>
<td>Enalapril</td>
<td>73</td>
<td>Female</td>
<td>10 days</td>
<td>Fatigue, vomiting</td>
<td>Mixed</td>
<td>Normalization</td>
<td>Valle et al. 26</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>?</td>
<td>Male</td>
<td>?</td>
<td>?</td>
<td>Hepatocellular&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Normalization</td>
<td>Hilburn et al. 27</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>64</td>
<td>Female</td>
<td>12 days</td>
<td>Jaundice, aplastic anemia</td>
<td>Hepatocellular</td>
<td>Death due to sepsis</td>
<td>Harrison et al. 28</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>56</td>
<td>Male</td>
<td>4 months</td>
<td>Jaundice, pruritus, fatigue</td>
<td>Hepatocellular</td>
<td>Chronification</td>
<td>Droste and de Vries 29</td>
</tr>
<tr>
<td>Enalapril</td>
<td>46</td>
<td>Male</td>
<td>3 years</td>
<td>Malaise, jaundice</td>
<td>Hepatocellular</td>
<td>ALF, LTX, postoperative death</td>
<td>Jeserich et al. 30</td>
</tr>
<tr>
<td>Enalapril</td>
<td>80</td>
<td>Female</td>
<td>30 days</td>
<td>Jaundice</td>
<td>Cholestatic</td>
<td>ALF, death</td>
<td>Gonzalez de la Puente et al. 31</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>61</td>
<td>Male</td>
<td>5 weeks</td>
<td>Asthenia, jaundice, pruritus, nausea</td>
<td>Cholestatic</td>
<td>Chronification</td>
<td>Nunes et al. 10</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>43</td>
<td>Male</td>
<td>3 months</td>
<td>Pruritus, jaundice, abdominal pain</td>
<td>Cholestatic</td>
<td>Normalization</td>
<td>Romero-Gomez et al. 32</td>
</tr>
<tr>
<td>Enalapril</td>
<td>66</td>
<td>Female</td>
<td>4 weeks</td>
<td>?</td>
<td>Cholestatic</td>
<td>Normalization</td>
<td>Hartleb et al. 33</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>74</td>
<td>Female</td>
<td>3 days</td>
<td>Jaundice</td>
<td>Cholestatic&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Normalization</td>
<td>Schoondyk et al. 34</td>
</tr>
<tr>
<td>Enalapril</td>
<td>58</td>
<td>Male</td>
<td>2 years</td>
<td>Jaundice, abdominal pain, dark urine, anorexia</td>
<td>Mixed</td>
<td>Normalization</td>
<td>Macias et al. 35</td>
</tr>
<tr>
<td>Enalapril</td>
<td>7</td>
<td>Female</td>
<td>4 years</td>
<td>Jaundice, bilateral pretibial edema, ascites</td>
<td>Cholestatic</td>
<td>Normalization</td>
<td>Bas et al. 36</td>
</tr>
<tr>
<td>Ramipril</td>
<td>51</td>
<td>Male</td>
<td>1 month</td>
<td>Anorexia, jaundice, pruritus</td>
<td>Cholestatic</td>
<td>Chronification</td>
<td>Yeung et al. 11</td>
</tr>
<tr>
<td>Ramipril</td>
<td>59</td>
<td>Male</td>
<td>2 months</td>
<td>Jaundice, nausea, pruritus</td>
<td>Cholestatic</td>
<td>Normalization</td>
<td>Yeung et al. 11</td>
</tr>
<tr>
<td>Ramipril</td>
<td>51</td>
<td>Male</td>
<td>3 weeks</td>
<td>Asymptomatic</td>
<td>Unclassifiable&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Normalization</td>
<td>Yeung et al. 11</td>
</tr>
<tr>
<td>Enalapril</td>
<td>62</td>
<td>Female</td>
<td>?</td>
<td>Maculopapular rash, fever, pneumonitis</td>
<td>Mixed</td>
<td>Normalization</td>
<td>Maimon et al. 37</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>78</td>
<td>Male</td>
<td>1 month</td>
<td>Jaundice, pruritus, poor appetite, nausea, dark urine</td>
<td>Cholestatic</td>
<td>Normalization</td>
<td>Chou et al. 36</td>
</tr>
<tr>
<td>Enalapril</td>
<td>44</td>
<td>Male</td>
<td>2.5 years</td>
<td>Jaundice, hepatic encephalopathy</td>
<td>Cholestatic</td>
<td>Normalization</td>
<td>da Silva et al. 38</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>30</td>
<td>Female</td>
<td>8 months</td>
<td>Jaundice</td>
<td>Hepatocellular</td>
<td>Normalization</td>
<td>Zalawadiya et al. 40</td>
</tr>
</tbody>
</table>

Abbreviations: ALF, acute liver failure; LTX, liver transplantation.

*Pattern of liver injury depends on the ratio of the relative rise of alanine aminotransferase (ALT), as a multiple of its upper limit of normal, to the relative rise of alkaline phosphatase (ALP). Cholestatic drug-induced liver injury (DILI) has a ratio <2, mixed DILI has a ratio of 2–5, and hepatocellular DILI has a ratio >5. When values were missing, the liver biopsy was considered.

<sup>1</sup>ALT value missing, grading derived from liver biopsy.
<sup>2</sup>ALP value missing, grading derived from liver biopsy.
<sup>3</sup>ALT value missing, no liver biopsy.
<sup>4</sup>ALT and ALP values missing, grading derived from liver biopsy.
<sup>5</sup>ALP value missing, no liver biopsy.
<sup>6</sup>Re-exposure with positive rechallenge.

Method, which illustrates another, liver-specific way of classifying DILI into “highly probable,” “probable,” “possible,” or “unlikely.” A score of 12 of 15 possible points was reached, and the case was classified as “highly probable,” which supported further the results derived from the WHO-based assessment.

The patient presented with jaundice and highly elevated liver enzymes (both ALT and ALP). This constellation makes the case consistent with the results of our FAERS research, as jaundice and elevation of liver enzymes were the hepatic adverse events reported the most in cases of ramipril-induced liver injury. Interestingly, these adverse effects...
The mixed type of DILI presented by our patient is consistent with the findings from the literature concerning ACEI hepatotoxicity, which are summarized in Table 1, with respective cases occurring even after several years.

The mixed type of DILI presented by our patient is contrary to the other 3 suggested cases of ramipril-associated DILI from the literature (twice cholestatic, once unclassifiable). Altogether, cholestasis seems to be the dominating pattern of ACEI-induced liver injury, excluding lisinopril. The reason for the persistent hepatocellular pattern of lisinopril-induced liver injury is unknown. Differences in the molecular structure do not seem to be of major importance, as dicarboxylic acid-containing ACEIs other than lisinopril (e.g., enalapril) have only rarely been associated with hepatocellular injury. Variations among ACEIs concerning selectivity for bradykinin binding sites may be a possible explanation. ACEIs inhibit kininase II, leading to an increased bradykinin activity and subsequently to an increased conversion of arachidonic acid to prostaglandins and leukotrienes. Prostaglandins are important for hepatobiliary function because some of them can decrease bile flow and therefore induce ACEI-associated cholestasis. On the other hand, leukotrienes seem to exhibit hepatocellular toxicity themselves.

We present the first case of ramipril-induced liver injury proven by positive rechallenge. Despite the relative rareness of ACEI-associated hepatotoxicity, ramipril should be considered as a possible etiology in case of acute onset jaundice or acute elevation of liver enzymes, in particular when common causes such as viral hepatitis or cholangitis can be ruled out. The pattern of liver injury will probably include cholestasis, but hepatocellular damage may also appear. Regular monitoring of liver enzymes does not appear useful because time to onset can be very variable.

**DISCLOSURE**

R.K. has consultant/advisory arrangements with Bayer Pharma, Berlin-Chemie, Daiichi, and BMS. E.G. has consultant arrangements with Bayer AG, Novartis, and Teva and has received grant/research support from Bayer AG and Novartis. All other authors declared no conflict of interest.

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Ramipril-induced Liver Injury


