A reoccurring drug induced liver injury (DILI) with cetirizine and amoxicillin–clavulanate potassium

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A 35-year-old woman with acute otitis media was treated with amoxicillin 1 g every 8 hours for 8 days. It was switched to amoxicillin–clavulanate potassium 875/125 mg every 8 hours for four days because of lack of response. When the patient finished the course of antibiotics she experienced general malaise, nausea, dark urine, and acholia. On physical examination she displayed jaundice. The patient denied any history of alcohol intake, use of recreational drugs and other medication (prescription, over-the-counter or herbal preparations). She had no known drug allergies or underlying diseases. Laboratory blood tests showed an increase in levels of aspartate aminotransferase (AST): 1798 IU/mL, alanine aminotransferase (ALT): 2130 IU/mL, alkaline phosphatase (ALP): 132 IU/L, gammaglutamyltranspeptidase (GGT): 118 IU/L, total bilirubin (TBL): 6.31 mg/dL and direct bilirubin: 1.31 mg/dL. The leukocyte count was normal, with no eosinophilia. Glucose levels, thyroid hormones, proteinogram and prothrombin index were not altered. Antinuclear antibodies (ANA) up to 1/320 with a negative anti-smooth muscle antibody (SMA) and anti-liver kidney microsomal antibody (anti-LKM). Serological tests for hepatotropic viruses (IgM anti-HAV, HBsAg, IgM anti-HBc, anti-HCV, HCV RNA) and anti-HIV were negative. An abdominal ultrasound examination indicated a normal liver with normal biliary tract. The episode was attributed to the amoxicillin–clavulanate potassium treatment. This causality obtained a score of 7 (probable) using the updated scale of the Roussel Uclaf Causality Assessment Method (RUCAM/CIOMS)\(^1\).

The patient had recovered completely three weeks after stopping treatment and values for liver function had returned to normal.

Thirteen years earlier, the patient suffered a similar episode with general jaundice and laboratory blood tests showing an increase in AST (1873 IU/mL), TBL (8.82 mg/dL) and an

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**Key words:** Drug-induced liver injury. Cetirizine. Amoxicillin–clavulanate potassium. Hepatotoxicity.

**Palabras clave:** Enfermedad hepática tóxica inducida por drogas. Cetirizina. Amoxicilina/clavulanato de potasio. Hepatotoxicidad.
International normalized ratio (INR) of 2.09. On that occasion, the patient required hospital admittance due to severe liver impairment. ANA up to 1/160 with negative SMA and anti-LKM. Other causes of liver injury were excluded (IgM anti-HAV, IgM anti-HBc, anti-HCV, HCV RNA, IgM CMV and IgM EB were negative with normal thyroid hormones and proteinogram) and ultrasonographic examination was normal. The score of RUCAM/CIOMS scale was 7. She was diagnosed of acute hepatitis due to an unknown cause.

On that occasion the only treatment involved was cetirizine 10 mg. The patient had started treatment with this antihistamine a month before due to seasonal allergic rhinoconjunctivitis and cetirizine was withdrawn when she was admitted to the hospital. The evolution was correct with analytical normalization at six weeks that was subsequently confirmed. The only medication she reported to have taken between the two episodes was naproxen very sporadically.

According to the findings and the RUCAM/CIOMS scale, the patient was diagnosed with drug induced liver injury (DILI) probably secondary to amoxicillin–clavulanate potassium and cetirizine.

The analytical evolution of the two DILI episodes can be seen in table 1.

Liver injury can be induced by several different causes (infections, toxic substances, autoimmunity, drugs, etc). DILI is considered when a possible culprit drug is present and other causes of liver injury have been excluded. For this diagnosis, one of the following three criteria must be fulfilled: (1) ALT ≥ 5 times the upper limit of normal (ULN), (2) ALP ≥ 2 times ULN, (3) ALT ≥ 3 times ULN plus total bilirubin ≥ 2 times ULN

Although hepatotoxicity has been described with virtually all drugs, DILI represents less than 1% of cases of acute liver injury. An incidence of 13.9 to 19.1 cases per 100,000 inhabitants has been reported. In a broad review of DILI published series, the authors found that 34.2% of cases of suspected DILI had alternative causes of liver injury that confound the DILI diagnosis. They suggest that DILI diagnosis should be established using a score system such as the RUCAM/CIOMS scale. Although this scale has its limitations, it can sometimes help establish the causality in DILI. In the case of our patient, other causes of liver injury were excluded and the RUCAM/CIOMS scale indicated a causality level of probable in both episodes.

Susceptibility to DILI is believed to be the result from interplay of multiple factors, including those related to the structure of the drug, patient’s genetic background, the influence of underlying diseases, and associated medications. Nevertheless, a genetic base of DILI has not been determined.
In our case, taking into the account the positive results of ANA in both episodes, we suspect a possible involvement of an autoimmune mediated mechanism not yet clarified. Lucena et al\(^7\) reviewed all registered cases of DILI in Spain for a period of 15 years. The frequency of individuals experiencing two DILI episodes caused by different drugs was 1.21%. The researchers found that second episodes of DILI were more likely to be associated with features of autoimmune hepatitis; however, it remained uncertain if this was drug-induced unmasking of true autoimmune hepatitis or DILI with an autoimmune component. Also, only in two cases drugs were not related in structure or function, as it happened to our patient: she first had a DILI due to cetirizine and then a second episode of DILI a few years later due to amoxicillin–clavulanate potassium. According to the US DILI Network\(^8\) and other publications\(^3\) the major category of drugs causing DILI are anti-infectious, with amoxicillin-clavulanate being the most prominent one\(^8\). It should be noticed that amoxicillin, without clavulanate, does not appear at the top ten major individual agents causing DILI\(^8\). However, less than 10 cases have been reported in the literature of cetirizine related acute hepatitis\(^10\).

The physiopathology of the DILI mechanism is not yet known, and as a result a specific diagnostic test could not be performed. It is debated weather reintroducing the suspected drug would reproduce the same liver damage.

Finally, the patient was advised to avoid both medications. For future prescriptions, including other antibiotics and antihistamines, we recommended to monitor liver function during the administration and the following weeks.

Recurrent DILI caused by different chemical drug structures is very rare. To our knowledge this is the first case of a reoccurring DILI with two different drugs: amoxicillin–clavulanate and cetirizine.

**Bibliography**


### Table 1. Evolution of the patient’s liver test in the two episodes of DILI.

<table>
<thead>
<tr>
<th></th>
<th>DILI 1</th>
<th>DILI 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Jun 12&lt;sup&gt;th&lt;/sup&gt;</td>
<td>Jun 16&lt;sup&gt;th&lt;/sup&gt;</td>
</tr>
<tr>
<td>ALT (N≤34 IU/L)</td>
<td>1,873</td>
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<tr>
<td>AST (N≤30 IU/L)</td>
<td>1,500</td>
<td>1,260</td>
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<td>BT (N≤1 mg/dL)</td>
<td>8.8</td>
<td>18.6</td>
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<td>GGT (N≤26 IU/L)</td>
<td>64</td>
<td>72</td>
</tr>
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<td>ALF (N≤104 IU/L)</td>
<td>120</td>
<td>120</td>
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<tr>
<td>INR (N ≤ 1.2)</td>
<td>2.0</td>
<td>1.7</td>
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