An analysis of the causes, characteristics, and consequences of reexposure to a drug or compound responsible for a hepatotoxicity event


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ABSTRACT

Introduction: reexposure to a causal agent represents a potentially serious event in hepatotoxicity. Objectives: to assess the characteristics and outcome of cases with positive reexposure. Material and methods: a retrospective study of cases with evidence of positive reexposure included in Registro Español de Hepatopatías Asociadas a Medicamentos, and an analysis of their relation to demographic and clinical variables, causality, course, and consequences. Results: of a total of 520 cases 31 (6%) met reexposure criteria. Fatal outcomes, needs for admission, and mean recovery time were all higher for hepatocellular-type toxic injury. The most commonly identified drug class was antibiotics. On most occasions (73%) reexposure to the causal compound escaped notice because of: absence of index case diagnosis, lack of information to patients and their physicians, and (12%) development of cross reactions between structurally similar drugs. Conclusions: accidental reexposure to a drug or a structurally-related compound after an initial hepatotoxicity event is common and may have serious consequences, particularly in hepatocellular-type toxicity. Careful history taking and reflecting diagnostic suspicion in the initial episode’s record may reduce the incidence of this iatrogenic event.

Key words: Reexposure. Hepatotoxicity. Drug-induced liver disease. Hepatic adverse events.

RESUMEN

Introducción: la reexposición al agente causal constituye un incidente potencialmente grave en hepatotoxicidad. Objetivos: evaluar las características y la evolución de los casos con reexposición positiva. Material y métodos: estudio retrospectivo de una serie de casos con evidencia de reexposición positiva incluidos en el Registro Español de Hepatopatías Asociadas a Medicamentos, analizando su relación con variables demográficas y clínicas, causalidad, evolución y consecuencias. Resultados: de un total de 520 casos, 31 (6%) cumplían los criterios de reexposición. La evolución fatal, la necesidad de hospitalización y el tiempo medio de recuperación fueron mayores en la lesión tóxica de tipo hepatoceleular. El grupo farmacológico identificado con mayor frecuencia fue el de los antibióticos. En la mayoría de los casos la reexposición con el compuesto responsable fue inadvertida (73%) debido a: la ausencia de diagnóstico del caso índice, la carencia de información al paciente o a su médico y también (12%) por el desarrollo de una reacción cruzada entre fármacos estructuralmente similares. Conclusiones: la reexposición accidental a un mismo fármaco o a otro estructuralmente relacionado tras un primer episodio de hepatotoxicidad no es infrecuente y sus consecuencias pueden ser graves, especialmente en el tipo de lesión hepatoceleular. Una minuciosa historia clínica y la sospecha diagnóstica reflejada en el informe del primer episodio podrían disminuir la incidencia de este evento iatrogénico.

INTRODUCTION

Liver toxicity, defined as liver injury or damage resulting from exposure to a prescription drug or other chemical agent, is particularly significant given its potential severity, and represents a most common cause of drug withdrawals in Europe and the United States (1,2). While no consistent incidence or prevalence figures are available for liver-related adverse events, toxicity is estimated to account for 4-10% of jaundice episodes admitted to general hospitals (3-5), but in a recent study most cases derived from acetaminophen intoxication, with cases due to idiosyncratic hepatotoxicity representing only 0.7% (5). A prospective population-based study in a French region estimated a yearly incidence rate of 14 cases of liver toxicity per 100,000 population, with an overall standardized incidence of 80 cases per million inhabitants per year (6). Antibacterials, non-steroidal anti-inflammatory drugs, and pain killers are most commonly implicated in reported series (7).

Since no specific markers will allow us to confirm the presence of liver toxicity, diagnosis may become very challenging and requires a high index of clinical suspicion (8). Liver toxicity screening requires thorough history taking, the ruling out of other causes of liver injury, and an understanding of generic risk factors for hepatotoxicity development. A most important criterion for the diagnosis of liver toxicity is liver injury relapse upon re-exposure (rechallenge) to a suspect drug, which is considered by some authors the gold standard in the diagnosis of liver toxicity (9). Positive rechallenge is defined as an increase in ALT (hepatocellular injury) and AP (cholestatic lesion) values above twice the upper limit of normal following drug re-exposure.

However, such rechallenge with a drug allegedly implied in a hepatotoxicity event is not indicated for diagnostic purposes on ethical grounds, and may also yield false negative results (10). Therefore, such reexposure testing would only be warranted for exceptional cases in which the drug involved is essential, and provided that the patient has been briefed on the entailed risks and his written consent has been obtained. The present study represents the first analysis in the literature of an extensive series with evidence of positive rechallenge according to reexposure circumstances, demographic variables, drug class, treatment duration and range, indication, liver injury type, presence of hypersensitivity manifestations, comorbidities, risk factors, and outcome.

MATERIAL AND METHODS

Data were obtained from Registro Español de Hepatopatías Asociadas a Medicamentos, which was founded in 1994 and is co-ordinated by two of the present authors (R. J. Andrade and M. I. Lucena). Patients with positive reexposure in the registry were identified, with reexposure being defined as twice greater ALT and AP levels for hepatocellular and cholestatic/mixed cases, respectively, following readministration. Some cases included in this study have been previously reported as single-case or case-series reports (11-16).

Registry operation, data collection, and causality assessment methods have already been published in detail (13,16). Data were collected as per a structured protocol containing the following codes: Time relationship between drug use or reexposure and liver disease onset, and between suspect agent discontinuation and liver dysfunction improvement or recovery; exclusion of other liver conditions; presence of known risk factors for liver toxicity such as alcohol consumption (amount given as grams after volume conversion) or pregnancy; and liver damage outcome. Currently and previously used drugs were thoroughly reviewed, as were herbal remedies and potential toxins. Other causes of liver disease were excluded: Recent viral hepatitis A (anti-HAV IgM), B (anti-HBV IgM) or C (anti-HCV and RNA+ with PCR), autoimmune diseases (ANA, anti-mitochondrial antibodies, anti-smooth muscle antibodies), and bile obstruction (abdominal sonography with add-on magnetic resonance imaging or endoscopic cholangiography when needed). When suggested by the clinical setting cytomegalovirus, Epstein-Barr virus, herpes virus, and hepatitis E virus were all ruled out; serologic tests for bacteria such as Salmonella, Campylobacter and Listeria were also performed. Patients younger than 40 years had their ceruloplasmin and urinary copper excretion measured to rule out Wilson’s disease. Similarly the presence of other metabolic liver conditions was assessed, including hemochromatosis, alfa-1 antitrypsin deficiency, and –in patients with a recent history of hypotension– ischemic hepatitis. Uncertain cases such as patients with positive autoimmunity markers, alcoholism, prior liver disease, or systemic conditions with potential liver involvement underwent liver biopsy for more information on their etiology.

Cases were reviewed by the attending physician, and then assessed by three independent experts from the coordinating center, who assessed causality initially using
their clinical judgment and then by using the Council for International Organizations of Medical Sciences (CIOMS) scale, also designated Roussel-Uclaf Causality Assessment Method (RUCAM) (17,18). This scale is based on a standardized scoring system taking several criteria into account (timing, outcome, risk factors, concomitant drugs, exclusion of alternative, non-pharmacologic causes, prior information on drug-related liver toxicity, reexposure), and the final result is translated into suspicion categories: Definite or highly probable (> 8 points), probable (6-8 points), possible (3-5 points), unlikely (< 2 points), and excluded (≤ 0 points). Only cases scored as possible, probable or definite using the CIOMS scale were included in the database.

Lesion type definition and classification were established by applying the criteria derived from the International Consensus Group meeting (19). Biochemical changes following reexposure that failed to rise above twice the upper limit of normal were considered biological. Liver injury was defined as an increase in ALT or conjugated bilirubin equal to twice the upper limit of the normal range; or a combined increase in AST, alkaline phosphatase (AP) and total bilirubin, with one of them reaching above two times the ULN. Lesions were classified based on pathological findings or alternatively biochemical findings in the absence of biopsy. Liver damage was deemed hepatocellular for ALT/FA rations > 5, cholestatic for values < 2, and mixed for levels > 2 and < 5. For this categorization initial laboratory levels were used. Finally, an attempt at establishing the pathogenetic mechanism for liver damage was made by considering it either intrinsic or idiosyncratic, the latter being further classified as immunoallergic in the presence of evidence for hypersensitivity, including fever, rash, and presence of eosinophils in the blood or a liver biopsy sample.

Drugs responsible for liver reactions were classified according to the Anatomical Therapeutic Classification (ATC) recommended by WHO-Europe (20).

Data obtained were analyzed using SPSS (Statistical Package for the Social Sciences, version 10.0 for Windows). A descriptive analysis was made, and the chi-squared test was used. Differences were considered statistically significant when p values were smaller than 0.05.

RESULTS

Among a total of 520 cases of liver toxicity in Registro Regional de Hepatotoxicidad, 33 had a history of reexposure to the substance responsible for a prior event. Of these, 2 patients did not meet the criteria for positive reexposure, as changes were considered biological in nature, which led to their exclusion from the analysis. A total of 31 cases (6%) thus met the defined criteria. Table I shows the main demographic and clinical characteristics of patients included in the registry with prior liver toxicity and readministration events either using the imputed drug or a substance within the same drug class.

Twenty-two patients (71%) in our series had hepatocellular injury, and nine had cholestatic or mixed damage (29%). Table II describes the various variables, both qualitative and quantitative, associated with the different liver injury types in cases of positive reexposure. Mean age was 42 years (42 years in the hepatocellular group and 47 years in the cholestatic/mixed group); 48% were males (45% in the hepatocellular group and 55% in the cholestatic/mixed group).

Mean treatment duration was longer for hepatocellular lesions –100 vs. 87 days. Duration was shorter for second events following reexposure for both liver injury types (Table II). Twelve patients (39%) had hypersensitivity evidence (eosinophilia, rash or fever). Biochemical findings were as follows: Mean ALT was 998 IU/dL during the first event, and 812 during reexposure; alkaline phosphatase results were 275 IU/dL initially, and 265 IU/dL during the second event; mean bilirubin was 11.09 mg/dL during the index episode and 6.31 mg/dL after rechallenge.

As regards severity, 16 patients required hospitalization (52%), 12 of them with hepatocellular damage (55%) and 4 with cholestatic/mixed (44%) damage. Three patients admitted with hepatocellular injury had a fatal outcome –2 died from liver failure, and 1 was transferred to a hospital with a transplant program after developing fulminant liver failure. A patient in the cholestatic/mixed group also had acute liver failure requiring a liver transplant.

Eleven patients underwent percutaneous liver biopsy, with results being listed in table I. The most common histologic lesion was cholestatic hepatitis (5 cases) followed by hepatocellular necrosis in 4 patients. One patient had centrolobular necrosis. Finally, the biopsy performed to the patient suspect of liver toxicity secondary to estradiol showed nonspecific changes.

Anti-infectious agents were the most commonly identified class (8 cases, 26%), followed by nervous system and cardiovascular drugs (5 cases, 16% each). The antibiotic amoxicillin-clavulanic acid was the most commonly involved drug. Three cases in the series resulted from new drugs available for fewer than three years at the time of the event –one was ebrotidin, which was eventually withdrawn because of its potential for liver toxicity (11,16).

Reexposure circumstances and causal drugs are listed in table III, which also includes the two patients with readministration of a drug responsible for a prior liver toxicity event but with no liver enzyme increase above twice the upper limit of normal. As may be seen, reexposure was accidental in 24 cases (73%) and circumstances were variable. Major causes of accidental rechallenge included absence of a definite diagnosis or of liver toxicity suspicion after the initial event in 21 cases (64% of total), and failure to inform patients or their attending practitioners in three cases (9% of total). On the other hand,
DISCUSSION

The present study identified 33 patients with a history of reexposure to a drug allegedly involved in a prior liver toxicity event from all 520 cases recorded in Registro Español de Hepatotoxicidad at the time of the study. Of these, 31 patients met positive reexposure criteria, which represent 6% of all patients in the registry, a non-negligible figure given its potential impact and the fact that this should be preventable in most cases.

Among reexposure episodes hepatocellular injury was predominant, and entailed a poorer prognosis with a higher number of hospital admissions and a more common progression to transplant or death. Such findings are in accordance with results from an overall analysis on the whole registry (7). This group of patients did have, however, a higher percentage of hypersensitivity manifestations (39%) when compared to the overall registry analysis, which identified evidence of allergy in 23% of cases (13). Furthermore, even considering the small number of patients with reexposure in the cholestatic/mixed group, the frequency of cases with evidence of allergy was high, which suggests that this pathogenetic mechanism is most commonly expressed as a cholestatic/mixed injury pattern. Similarly, it should be highlighted that while one third of patients in the series underwent liver biopsy, findings were generally inconclusive for a diagnosis of liver toxicity, since the reexposure event had a greater impact itself. Under reexposure circumstances biopsy

Table I. Demographic and clinical data from cases of liver toxicity with positive reexposure included in the hepatotoxicity registry

<table>
<thead>
<tr>
<th>Sex</th>
<th>Drug</th>
<th>Age (days)</th>
<th>Drug (days)</th>
<th>Duration (days)</th>
<th>TB (mg/dL)</th>
<th>ALT1 (ULN)</th>
<th>ALT2 (ULN)</th>
<th>PAT1 (ULN)</th>
<th>PAT2 (ULN)</th>
<th>Damage type</th>
<th>Bioty</th>
<th>CIOMS/RUCAM</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>23F</td>
<td>Mesalazine</td>
<td>210</td>
<td>190</td>
<td>275</td>
<td>1</td>
<td>4.2</td>
<td>4.7</td>
<td>0.55</td>
<td>0.6</td>
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<td>Hospitalization</td>
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</tr>
<tr>
<td>53M</td>
<td>Laronazocine</td>
<td>(11)</td>
<td>58</td>
<td>58</td>
<td>6</td>
<td>2.5</td>
<td>1.2</td>
<td>-</td>
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<td>Highly probable(10)</td>
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<tr>
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<td>180</td>
<td>185</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td></td>
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</tr>
<tr>
<td>17F</td>
<td>Chlorphenol</td>
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<td>137</td>
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<td>5.4</td>
<td>29.6</td>
<td>0.9</td>
<td>-</td>
<td>-</td>
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<td>Probable</td>
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<tr>
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<td>Astanaminophen (12)</td>
<td>18</td>
<td>1</td>
<td>14</td>
<td>26.3</td>
<td>7.1</td>
<td>5.1</td>
<td>-</td>
<td>-</td>
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<td>Hospitalization, HS</td>
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<tr>
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<td>152</td>
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<td>18</td>
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<td>1.2</td>
<td>0.7</td>
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<td>Highly probable(6)</td>
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<td>14</td>
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<tr>
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<td>Amox.-clav. (13)</td>
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<td>5</td>
<td>4</td>
<td>10</td>
<td>34.3</td>
<td>18.6</td>
<td>1.1</td>
<td>3</td>
<td>Cholestatic hepatitis</td>
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<td>Hospitalization, LT, HS</td>
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</tr>
<tr>
<td>23F</td>
<td>Camellia sinesis (14)</td>
<td>19</td>
<td>21</td>
<td>11</td>
<td>31.1</td>
<td>71.1</td>
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<td>1.01</td>
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<td>Hepatocellular necrosis Highly probable(11)</td>
<td>Hospitalization, F, HS</td>
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<td>-</td>
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<td>-</td>
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<td>Hospitalization, death, autolysis</td>
<td></td>
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<tr>
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<td>Etymoroycin</td>
<td>8</td>
<td>1</td>
<td>2.2</td>
<td>5.3</td>
<td>-</td>
<td>1.7</td>
<td>-</td>
<td>MIX</td>
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<td>HS</td>
<td></td>
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<tr>
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<td>23</td>
<td>1</td>
<td>4</td>
<td>7.4</td>
<td>6.4</td>
<td>34.2</td>
<td>1.4</td>
<td>0.5</td>
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<td>Hospitalization, HS</td>
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<tr>
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<td>40</td>
<td>15</td>
<td>90</td>
<td>15</td>
<td>3.8</td>
<td>22.2</td>
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<td>3.4</td>
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<td>Hospitalization, HS</td>
<td></td>
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<tr>
<td>49M</td>
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<td>3</td>
<td>15</td>
<td>6.6</td>
<td>-</td>
<td>515</td>
<td>-</td>
<td>3</td>
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<td>Hospitalization</td>
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<tr>
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<td>-</td>
<td>7.4</td>
<td>-</td>
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<td>1.4</td>
<td>HC</td>
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<td>8</td>
<td>14</td>
<td>10</td>
<td>7.5</td>
<td>2.2</td>
<td>-</td>
<td>7.1</td>
<td>-</td>
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<td>HS</td>
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<td>Estradiol</td>
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<td>195</td>
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<td>2.4</td>
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<td>MIX</td>
<td>Non-specific</td>
<td>Probable(6)</td>
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<td>Interferon</td>
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<td>7</td>
<td>121</td>
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<td>27.8</td>
<td>15.1</td>
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<td>1.8</td>
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<td>Paphagophene</td>
<td>6</td>
<td>2</td>
<td>6</td>
<td>3.4</td>
<td>38.9</td>
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<td>Pypsinmine</td>
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<td>16</td>
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<td>Hospitalization, death</td>
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<td>17</td>
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<td>46.4</td>
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<td></td>
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<td>5</td>
<td>5</td>
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<td>-</td>
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<td>-</td>
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<td>Hospitalization, HS</td>
<td></td>
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<td>24F</td>
<td>Valproic acid</td>
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<td>-</td>
<td>60.5</td>
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<td>0.5</td>
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<td>Hospitalization, HS</td>
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<tr>
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<td>15</td>
<td>30</td>
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<td>1.8</td>
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<td>Hospitalization</td>
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<td>2</td>
<td>7</td>
<td>4.2</td>
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<td>Clopidogrel</td>
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<td>93</td>
<td>77</td>
<td>16</td>
<td>10.2</td>
<td>8.7</td>
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<td>Cholestatic hepatitis</td>
<td>Highly probable(10)</td>
<td>Hospitalization</td>
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<tr>
<td>49M</td>
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<td>3</td>
<td>11</td>
<td>4.2</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
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<td>Hospitalization</td>
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<td>77M</td>
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<td>1.07</td>
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<td>Biological change</td>
<td></td>
<td></td>
</tr>
<tr>
<td>52F</td>
<td>Diclofenac</td>
<td>23</td>
<td>23</td>
<td>38</td>
<td>9.8</td>
<td>62.5</td>
<td>57.8</td>
<td>-</td>
<td>1.6</td>
<td>HC</td>
<td>Highly probable(6)</td>
<td>Hospitalization, HS</td>
<td></td>
</tr>
<tr>
<td>69F</td>
<td>Amox-clav.</td>
<td>4</td>
<td>14</td>
<td>8</td>
<td>3.15</td>
<td>20.9</td>
<td>10.6</td>
<td>2.6</td>
<td>1.4</td>
<td>HC Highly probable(10)</td>
<td>Hospitalization</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ALT: Alanine aminotransferase; AMA: Anti-mitochondrial antibodies; ASMA: Anti-smooth muscle antibodies; ANA: Anti-nuclear antibodies; P: Pathology; AST: Aspartate aminotransferase; TB: Total bilirubin; Chol: Cholestatic; F: Female; PA: Alkaline phosphatase; FLF: Fulminant liver failure; HC: Hepatocellular; HS: Hypersensitivity; M: Male; ULN: Upper limit of normal; Mix: Mixed; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus.

five episodes (15%) occurred in patients with conditions for which the imputed drug was either crucial or the best alternative available, and in 4 cases (12%) the drug responsible for reexposure was not the initial one (but was in the same class), presumably giving rise to cross reactivity.
may primarily have prognostic value. In fact, in one event in response to bentazepam the biopsy sample was consistent with active chronic hepatitis, as was previously described for this drug (21). Biopsy was anyhow more commonly indicated for hepatocellular injury, probably because this type of lesion is rather nonspecific, and its linking with a toxic etiology is more challenging (23). It should also be pointed out that latency was shorter after reexposure than after the initial event.

The drug class most commonly involved in reexposure events was antibiotics, and this finding was consistent with the overall assessment of Registro de Hepatotoxicidad (7). This fact reflects that such events are not only associated with a specific drug class, but also result from drug use conditions (7,15).

On analyzing the circumstances under which reexposure occurred, a higher frequency of accidental readministration was seen as a result of no suspicion or definite diagnosis of liver toxicity (new drugs or herbal remedies), neglected transaminase increase after the initial exposure, lack of information to patients or their physicians, or an unusual liver toxicity expression for the involved drug. The latter was the case with the patient in this series who had liver toxicity secondary to acetaminophen—it was an idiosyncratic reaction with evidence of hypersensitivity, an exceptional fact that rendered its diagnosis challenging (12).

Another circumstance seen in this study was the inability to identify or attribute liver disease to the drug responsible for the initial event, particularly when several potentially hepatotoxic compounds had been administered. This is the case with diclofenac—the initial episode of liver injury was attributed to amoxicillin-clavulanic acid, which had been administered concurrently with this anti-inflammatory agent; a readministration of the culprit drug was thus not prevented, and liver disease relapsed.

A surprising, preventable fact that occurred in three cases in the series, and which resulted in the unintended readministration of the offending drug, was that neither patients nor their general practitioners received information or a report on the initial event. This we may illustrate with our case of valproic acid-induced liver toxicity, in which the patient changed physicians, and his new GP received no report on the initial event; this practitioner prescribed the offending anticonvulsant again, which led to recurring liver toxicity.
Finally, in four cases the drug responsible for the second event was different from that responsible for the initial episode. This underscores the need to be aware of potential cross reactions regarding liver toxicity when structurally related drugs are used (7).

Interestingly, intentional reexposure to an offending drug as a result of said drug being the only or best option for the patient’s underlying condition (one of the few ethically acceptable indications for intentional rechallenge) represented only 15% of cases.

Practical recommendations that may derive from this study include the importance of informing both patients and their physicians, and of writing a detailed clinical report for cases of liver toxicity in order to prevent unintentional reexposure should the patient change physicians. On the other hand, liver toxicity reporting should be encouraged, and extreme care should be taken with novel drugs and herbal remedies. Lastly, clinicians should be aware of potential cross reactivity between different drugs.

To conclude, we may assert that the impact of liver toxicity injuries because of reexposure to an offending drug or a structurally similar compound may be potentially serious, that some patients may need hospitalization or liver transplant, and that a fatal outcome is also possible. While a diagnosis is certainly difficult to reach given the absence of specific tests, a high level of clinical suspicion, careful assessments, and clear information to patients and their physicians are essential to prevent unintentional readministration in cases of drug-induced liver damage.

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We are grateful for the contribution of Mr. Ramón Hidalgo to the statistical analysis of data. This study was partly supported by a grant from Agencia Española del Medicamento and scholarship FIS 07/0980.

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REFERENCES