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Potentially hepatotoxic drugs are still being prescribed to liver disease patients under tertiary care: it is time to say enough

Todavía se recetan medicamentos potencialmente hepatotóxicos a pacientes con enfermedad hepática que reciben atención terciaria: es hora de decir basta

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Abstract

Introduction and aim: Drug-induced liver injury (DILI) manifests as a spectrum of clinical presentations that carries morbidity and mortality. Patients with chronic liver disease (CLD), particularly hospitalized, are at high risk for developing DILI. We aimed to investigate the use of potentially hepatotoxic drugs (PHD) in patients with CLD in a tertiary university hospital. **Materials and methods**: Adult (≥ 18 years-old) with CLD admitted to the hospital from January 2016 to December 2018 were evaluated regarding PHD, assessing the risk of DILI and liver enzymes behavior after exposure. **Results**: From 931 hospitalized patients with CLD, 291 (31.3%) were exposed to hepatotoxic drugs during their hospitalization. Of those, 244 (83.8%) were cirrhotic. The most frequent causes of liver disease were hepatitis C (41.2%), followed by alcohol (13.2%), hepatitis C/alcohol (11.7%) and non-alcoholic fatty liver disease (5.8%). Decompensated cirrhosis (46.7%) was the main reason for hospital admission. The most often prescribed PHD were antibiotics (67.7%), cardiovascular drugs (34.4%), neuromodulators (26.1%) and anesthetics (19.9%). After exposure, 113 patients (38.8%) presented significant elevated liver enzymes. Surprisingly, PHD were more often prescribed in GI/Liver unit (48.8%) followed by emergency/intensive care unit (28.5%). A total of 65 patients (22%) died, however in neither case was it possible to safely infer causal relationship among PHD, liver enzymes and death. **Conclusion**: PHD prescription is frequent in patients with CLD even in a tertiary university hospital and in the gastroenterology and hepatology department, exposing these patients to an additional risk.

Keywords: liver diseases, drug-induced liver injury, acute-on-chronic liver failure, acute liver failure.

Resumen

Introducción y objetivo: La lesión hepática inducida por fármacos (DILI) se manifiesta como un espectro de presentaciones clínicas que conlleva morbilidad y mortalidad. Los pacientes con enfermedad hepática crónica (EHC), en particular hospitalizados, tienen un alto riesgo de desarrollar DILI. Nuestro objetivo fue investigar el uso de fármacos potencialmente hepatotóxicos (FPH) en pacientes con EHC en un hospital universitario terciario. **Materiales y métodos**: Se evaluó la expossición a FPH en adultos (≥ 18 años) con EHC ingresados en el hospital entre enero de 2016 y diciembre de 2018, evaluando el riesgo de DILI y el comportamiento de las enzimas hepáticas tras la exposición. **Resultados**: De 931 pacientes hospitalizados con EHC, 291 (31,3%) estuvieron expuestos a fármacos hepatotóxicos durante su hospitalización. De ellos, 244 (83,8%) eran cirróticos. Las causas más frecuentes de enfermedad hepática fueron la hepatitis C (41,2%), seguida del alcohol (13,2%), la hepatitis C / alcohol (11,7%) y la enfermedad del hígado graso no alcohólico (5,8%). La cirrosis descompensada (46,7%) fue el principal motivo de ingreso hospitalario. Los FPH más prescritos fueron antibióticos (67,7%), fármacos cardiovasculares (34,4%), neuromoduladores (26,1%) y anestésicos (19,9%). Tras la exposición, 113 pacientes (38,8%) presentaron elevación significativa de las enzimas hepáticas. Sorprendentemente, los FPH se prescribieron con mayor frecuencia en la unidad GI / Hígado (48,8%) seguido de la unidad de emergencia / cuidados intensivos (28,5%). Un total de 65 pacientes (22%) fallecieron, sin embargo, en ninguno de los casos fue posible inferir con seguridad la relación causal entre el FHD, las enzimas hepáticas y la muerte. **Conclusión**: la prescripción de FPH es frecuente en pacientes con EHC incluso en un hospital universitario terciario y en el servicio de gastroenterología y hepatología, exponiendo a estos pacientes a un riesgo adicional.

Palabras clave: enfermedad hepática, lesión hepática inducida por fármacos, insuficiencia hepática aguda sobre crónica, insuficiencia hepática aguda.

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Introduction

Drug-induced liver injury (DILI) manifests as a spectrum of clinical presentations that carries morbidity and mortality (1). The liver places a prime target for reactive metabolites of medicines as is central to removal of lipophilic drugs and presence of specific enzyme disposal pathway(s) of biotransformation (metabolism) (2). Establish the frequency of DILI worldwide associated with the clinical use of drugs is challenge due lack of consistent reporting systems and definitions (3). Thought, there is the acquiescence of increasing frequency of hepatic drug reactions due to the rise of prescriptions and the number of pharmacological agents available (4, 5).

Liver toxicity related to drugs have been divided into two varieties, based on the presumed mechanism of action of the chemical compound: intrinsic (direct or predictable) and idiosyncratic (indirect or unpredictable) (3). After the exposure to reactive metabolites, there are organelle stress and inflammation, resulting in necrosis and/or apoptosis of the hepatocyte or the induction of adaptive responses, with injury not occurring or being very mild. In the intrinsic DILI the process is determined by the individual drug and the hosts factors (especially genetic), with the role of innate and adaptive immune system (6). Intrinsic DILI is typically dose-related, onset is within a

short time span (hours to days), while idiosyncratic is usually not dose-related, and has a longer latency period (3).

Cirrhosis and chronic liver disease (CLD) not necessarily increases the risk of developing DILI (7, 8), however it is known based on systematic review of cohort studies that chronic hepatitis B and C are risk factors for DILI caused by anti- human immunodeficiency virus and anti-tuberculostatic therapy (9). Furthermore, DILI in patients with underlying liver disease arouse higher mortality (4). In cirrhotic patients most medications have not been thoroughly studied and specific prescribing information is often lacking; in those patients lower doses of medication are generally recommended based on pharmacokinetic change, despite limited data also in that subject (10). Acute hepatic lesion caused by drugs has been reported between 2% and 10% of patients hospitalized for jaundice (8). Hospitalized CLD patients are at high risk for developing DILI, however among those patients there is scant information on the pattern of medical prescription (10).

The diagnostic of DILI is a challenge for physicians, due the heterogeneous phenotypes (mild increase of liver enzymes (cholestatic, hepatocellular and mixed) to acute liver failure (ALF), absence of specific biomarkers and the need for diagnosis exclusion) (9). The greatest difficulty in research on DILI in patients with underlying liver disease is the distinction between additional liver injury caused by a medicine or progression of the underlying liver disease. Add to that the is sparing information on the pattern of potential hepatotoxic drugs in hospitalized liver disease patients (10). For that reason, we designed this retrospective study to investigate the prescribing patterns of potentially hepatotoxic drugs (PHD) in a Brazilian cohort of patients with CLD, and the demographic, clinical and laboratory characteristics.

Patients and methods

This retrospective study was conducted in adults (18 years or older), of both sex, with liver disease (cirrhotic or not) evaluated by hepatology department, at the Hospital de Clínicas of Porto Alegre, south Brazil, from January 2016 through December 2018. This study was approved by the Hospital de Clínicas of Porto Alegre Ethics Committee, and informed consent for review of medical records was not needed. We excluded patients with organ transplants (except isolated liver), carriers of human immunodeficiency virus and patients with missing data from electronic medical records. The acute-on-chronic liver failure (ACLF) was defined as recommendations of the Asian Pacific Association (11).

We access the patient's gender and age, length of stay and reason for hospitalization, sector of prescription in the hospital and class of drugs used, describing the most frequents. Antihypertensives, antianginals and antiarrhythmic were considered in the cardiovascular class. Anxiolytics, antidepressants and anticonvulsants were included in the class of neuromodulators. If the patient was cirrhotic, the etiology, Child Pugh and the model for end-stage liver disease (MELD) were analyzed, as well as cirrhosis decompensation at the moment of hospitalization. We described values of gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, creatinine and prothrombin time present in medical records before and after hospitalization and their highest values during it. The presence or absence of death during hospitalization was also analyzed.

Statistical analysis

The qualitative variables are shown in terms of absolute and relative frequencies in percentage. The continuous ones are expressed in terms of summary measures, mainly median with interquartile range or mean +/- EE (standard error). In the case of continuous variables, the normality test was studied with the Kolmogorov-Smirnov test. When the assumption was not fulfilled, it was analyzed with the non-parametric Friedman test for the comparison between three times. The association study between qualitative variables was carried out with Chi square test or Fisher's exact test in the cases of expected cells smaller than 5. In the case of statistical association, the corresponding association strength is calculated - Odds Ratio with its 95% Confidence Interval (CI). Non-parametric Mann-Whitney test was used to calculate differences between independent groups for each continuous variable of interest. We worked with an alpha significance value of 0.05. Statistical analysis has been performed with STATA v.12.0 software.

Results

In the analyzed period, 931 patients with CLD were hospitalized and a total of 291 patients (31.3%) were exposed to hepatotoxic drugs during their hospitalization, in the period from January 2016 through December 2018 at the Hospital de Clínicas of Porto Alegre. Of those, 53% were men, with an average age of 60 years. Cirrhosis were present in 83% of patients, and 3% presented ACLF. The most frequent reason for hospitalization was due to decompensated cirrhosis (46.7%), followed by hepatocellular carcinoma (18.6%).

The most frequent etiology of liver damage was hepatitis C (41.2%) followed by alcohol (13.4%), hepatitis C/alcohol (11.7%), non-alcoholic fatty liver disease (5.8%), hepatitis B (3.8%), cholestatic disease (3.4%) and autoimmune hepatitis (1.4%). In relation to the Child-Pugh score, the data was lacking for 54.6% of the patients. For those who had data, 29.5% (39 patients) were from group A, 43.2% (57 patients) from group B and 27.3% (36 patients) from group C. Information about variables used to calculate MELD score was available in 103/291. MELD ≤15 were present in 64 patients, MELD 16-30 in 33 patients, and MELD 31-46 in 6 patients. Regarding the cause of liver disease decompensation, 121 patients (41.6%) had ascites, 45 patients (15.5%) had gastrointestinal bleeding, 29 patients (10.0%) had spontaneous bacterial peritonitis, 77 patients (26.5%) had hepatic encephalopathy and 97 patients (33.3%) showed loss of kidney function. Liver disease without cirrhosis were 47 patients (17%) (table 1).

Table 1. Baseline characteristics of all patients, cause of chronic liver disease and drugs

Characteristics		N	N %
Gender	Woman	136	46.7
	Men	155	53.3
Clinical decompensation	Ascites	121	41.6
	Digestive Bleeding	45	15.5
	Spontaneous Bacterial Peritonitis	29	10
	Impaired kidney function	97	33.3
	Hepatic Encephalopathy (HE)	77	26.5
	ACLF	9	3.1
	Cirrhosis	244	83.8
Etiology of Chronic Liver disease	HCV	120	41.2
	Alcoholic disease	39	13.4
	HCV/alcoholic	34	11.7
	NAFLD	17	5.8
	HBV	11	3.8
	Cholestatic disease	10	3.4
	Autoimmune hepatitis	4	1,4
	HCV + NAFLD	1	0.3
	Other	36	12.3
	No data	14	4.8
Drug	Antibiotics	197	67.7
	NSAIDs	24	8.2
	Antifungal	21	7.2
	Antineoplastic	4	1.4
	Neuromodulators	76	26.1
	Antiviral	19	6.5
	Antithyroid	14	4.8
	Statins	18	6.2
	Antituberculosis	4	1.4
	Cardiovascular	100	34.4
	Anesthetics	58	19.9
Cause of hospitalization	Decompensated cirrhosis	136	46.7
	HCC	54	18.6
	Others	101	34.7
Department of diagnostic	Emergency/ICU	83	28.5
	Hospitalization GAS/HEP	142	48.8
	Hospitalization /Others	66	22.7
Death		65	22

ACLF, acute-on-chronic liver failure; HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, Non-alcoholic fatty liver disease; HCC hepatocellular carcinoma; GAS/HEP hepatology; NSAIDs, nonsteroidal anti-inflammatory drugs; ICU, intensive care unit.

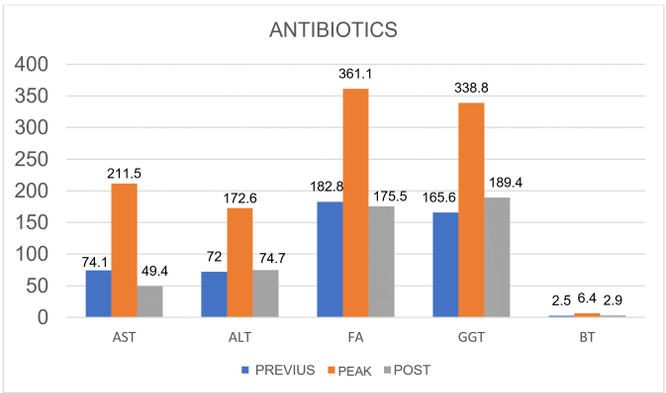
The most frequent sector of medication prescription was in the gastroenterology / hepatology department (48.8%) followed by emergency/ intensive care unit (28.5%). The most often prescribed PHD were antibiotics (67.7%), followed by cardiovascular drugs (34.4%), anesthetics (19.9%), non-steroidal anti-inflammatory drugs (NSAIDs) (8,2%), antifungal (7.2%), antiviral (6.5%), statins (6.2%), antithyroid (4.8), tuberculostatic drugs (1.4%) and antineoplastic agents (1.4%). (Table 1)

In regard to antibiotics, the average liver enzymes peak post-PHD exposition was 2.7 times upper limit of normality (ULN) of AST, 2.4 times ULN ALT, two times ULN of AP, two times ULN of GGT and 2.5 times of total bilirubin. About cardiovascular drugs, the average was five times ULN of AST, 3.7 times ULN of ALT, 3 times ULN of AP, 2.3 times ULN of GGT and 3.1 times ULN of total bilirubin. Concerning neuromodulators, the average laboratory post-PHD exposition was 3.4 times ULN of AST, 3 times

ULN of ALT, 1.2 times ULN of AP, 1.6 times ULN of GGT and 2 times ULN of total bilirubin. With regard to anesthetics drugs the average laboratory post-PHD exposition was 4.1 times ULN of AST, 3.6 times ULN of ALT, 3.6 times ULN of AP, 2.4 times ULN of GGT and 2.5 times ULN of total bilirubin; and for NSAIDs 2.8 times ULN of AST, 4.9 times ULN of ALT, 1.62 times ULN of AP, 2.6 times ULN of GGT and 3.1 times ULN of total bilirubin.

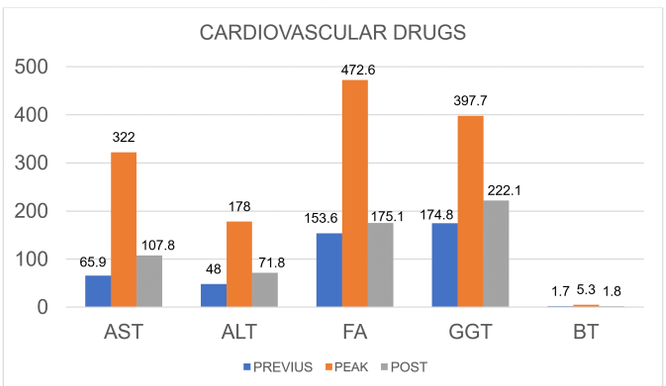
Figures 1 to 4 show the peak of laboratory abnormalities reached with the use of antibiotics, cardiovascular drugs, neuromodulators and anesthetics respectively.

Figure 1. Variation of mean values of liver biochemistries in patients who used Antibiotics



AST, aspartate aminotransferase; ALT, alanine aminotransferase; FA, fosfatase alcalina; GGT, gamma glutamyl transpeptidase; BT, bilirrubina total.

Figure 2. Variation of mean values of liver biochemistries in patients who used Cardiovascular drugs

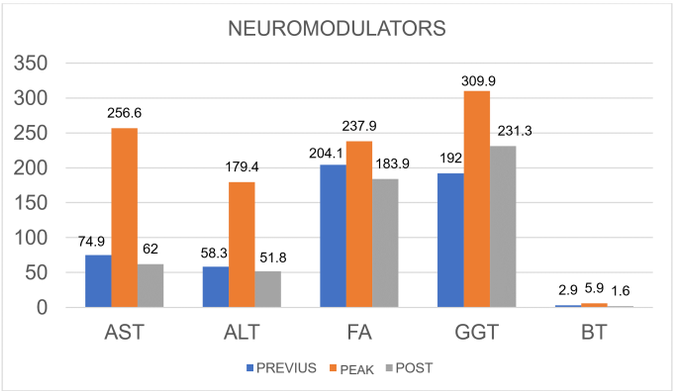


AST, aspartate aminotransferase; ALT, alanine aminotransferase; FA, fosfatase alcalina; GGT, gamma glutamyl transpeptidase; BT, bilirrubina total.

Regarding the group that received amoxicillin clavulanic, the average age and time of hospitalization were 56 years and 19 days respectively. Still regarding this agent, figure 5 shows the peak of laboratory abnormalities reached with the use of this drug.

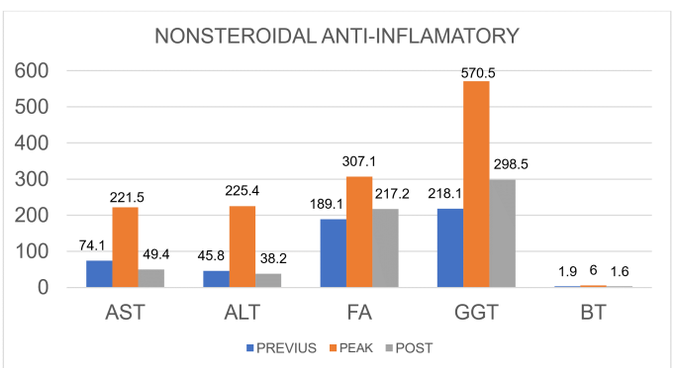
After drugs exposure, 113 patients (38,8%) had significant elevated liver enzymes. No statistically significant association was established between elevations of ALT (elevation of ≥5 ULN) or ALP (≥2 ULN) and accompanying elevations in concentrations of GGT, as elevation of ≥5 ULN ALT or ≥2 ULN ALP and the demographic characteris-

Figure 3. Variation of mean values of liver biochemistries in patients who used Neuromodulators agents



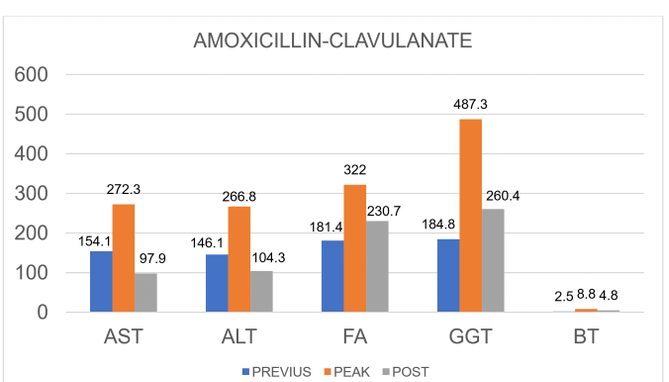
AST, aspartate aminotransferase; ALT, alanine aminotransferase; FA, fosfatase alcalina; GGT, gamma glutamyl transpeptidase; BT, bilirrubina total.

Figure 4. Variation of mean values of liver biochemistries in patients who used Nonsteroidal anti-inflammatory drugs



AST, aspartate aminotransferase; ALT, alanine aminotransferase; FA, fosfatase alcalina; GGT, gamma glutamyl transpeptidase; BT, bilirrubina total.

Figure 5. Variation of mean values of liver biochemistries in patients who used Amoxicillin-Clavulanate.



AST, aspartate aminotransferase; ALT, alanine aminotransferase; FA, fosfatase alcalina; GGT, gamma glutamyl transpeptidase; BT, bilirrubina total.

tics of the patients, the Child Pugh or the frequency of the group of drugs. A total of 67 patients (22%) died. The presence of ascites, hepatic encephalopathy and impaired renal function were associated with death (p-value< 0.05).

Of the 82 patients who received the antibiotic cefepime, 33 died (p-value< 0.001) and, of the 48 who received amoxicillin clavulanic 11 died (p-value 0.849).

Discussion

The drug therapy in patients with CLD is complex especially in cirrhotic patients due to the pathophysiological changes associated with the disease that alter the pharmacokinetics of drugs.(8) Patients with liver cirrhosis require close monitoring and dose adjustment to ensure rational use of medicines, to avoid the risk of DILI and other medicine-related problems.

This study described PHD utilization in a large cohort of CLD patients in a tertiary university hospital. We demonstrated that many patients with CLD received a potentially unsafe drugs during the study period (31.3%). This indicates the great magnitude of the results and illustrates the disregard for DILI in this population.

As stated at American College of Gastroenterology Clinical Guideline the use of potentially hepatotoxic drugs in patients with underlying liver disease should be based in risk versus benefit of the proposed therapy, with a case-by-case analysis (1). The guideline recommends advising the patients for cholestasis symptoms and abdominal pain; also monitor serum liver biochemistries at 4 – 6 week intervals, especially during the initial 6 months of treatment (1)(9). In our study, several drugs with hepatotoxic potential were used, such as NSAIDs, amiodarone and amoxi-clavulanate, even though other drugs with less hepatotoxic potential could have been used. This shows that the risk-benefit assessment was not always considered.

However the remaining drugs considered as potentially unsafe, such as betablockers, vasoactive drugs, and other antibiotics are life-saving drugs, particularly in patients admitted for decompensated cirrhosis. Thus, although it is very interesting to know the rate of DILI, the discussion of whether these drugs could have been avoided seems to be much more profound. Similarly, when considering admitted patients with severe underlying liver disease, perhaps confounders such as sepsis among others should be taken into account when evaluating transaminases and the impact of prescribed drugs.

Sex does not appear to be a risk for DILI (5, 12), however female patients with DILI seems to have a higher risk of ALF progression (13). Incidence of DILI appears to increase with age, this is also paralleled by an increase in medication use, suggesting that age per se might not be a risk for DILI (14). The Latin American DILI Network (LATINDILIN), a consortium of Latin American hepatologists that aim identification and characterization of DILI cases in Central and South America, described an average age of 50 years (11-91 years), and 61% female (15). A prospective study in a tertiary Egyptian hospital analyzed patients with CLD who presented DILI; of those 66.1% were men, and the mean age was 46.4 years ± 12.3 (16). In our study, median age was 60 years (51-66) and 53.3% of the patients were men.

Hepatitis C was present in 41.2% of patients, supported by other studies that show this infection as one of the main causes of CLD worldwide (17,18,19). In addition, when treatment of C virus with direct drugs agents is being carried out, it is necessary to take into account not only the possibility of hepatotoxicity of other drugs used during treatment, but also the risk of drug interaction (20).

It is interesting to note that 113 (38%) patients already had abnormal liver exams before starting treatment with hepatotoxic drugs and 88.5% of these patients were cirrhotic. Although we cannot adjudicate the hepatic changes due to these drugs, this suggests that attention is missing prescribe potentially hepatotoxic drugs in hospitalized CLD patients.

Most patients were cirrhotic, and ascites was present in 41.6% of them. Cirrhosis can affects drug absorption, distribution, bioavailability, cytochrome P450 metabolism and hepatic and renal clearance mechanisms, resulting in pharmacodynamic consequences (21). The presence of ascites can affect the volume distribution of drugs, bioavailability and elimination half-life (22).

The most used drug class in our study was antibiotics (67.7% of patients). In LATIDIN's DILI records, the most frequent drug classes were anti-infectives (32%), musculoskeletal agents (14%), antineoplastics (8.6%), sex hormones (8.2%), and central nervous system drugs (8.2%) whereas in the Spanish DILI Registry, anti-infectives (38%), central nervous system drugs (13%), musculoskeletal agents (11%), and cardiovascular drugs (10%) were the most represented. As for the isolated agent, amoxicillin-clavulanate was the most frequent in both records (15).

Amoxicillin clavulanate was used in 47 patients in our study. This drug is usually associated with a cholestatic pattern caused mostly by the clavulanic component, usually affects women, aged > 65 years and with previous report of this drug (24). Presentations regarding the use of this agent could be mild or severe, leading to ALF or urgent liver transplantation (25). The study by Lucena et al. suggests that amoxicillin clavulanate might be the most common cause of unpredictable hepatotoxicity in adults in Spain. The main pattern of lesion was hepatocellular, with age as the factor associated to development of cholestatic/mixed type of injury (26).

It is interesting that 47 patients received amoxicillin clavulanate, taking into account that its hepatotoxic potential is well known (category A), which implies more than 50 published cases. We believe that therapeutic alternatives with a lower hepatotoxic profile could and can be considered.

Cefepime, a fourth-generation cephalosporin, was another frequently prescribed antibiotic (82 patients). The cephalosporins is general associated with few hepatotoxicity cases, and only rare instances of DILI due to these agents have been published (27). The typical case of liver injury due to cephalosporins is self-limited cholestatic hepatitis with mild immunoallergenic features,

if it arises, 1 to 3 weeks after starting therapy, which sometimes occurs after a single parenteral dose. (28)

Cefepime is considered category D, with one to three cases of hepatotoxicity reported in the literature. Liao et al, describe a rare case of cefepime induced cholestasic liver injury. (29)

In the DILIN study carried out in the United States, 10% of individuals with DILI had pre-existing CLD, most of whom had hepatitis C, a mean age of 52 years, mostly women, mean ALT 689 U/l, AP 284 U/l, total bilirubin 13 mg/dl, international standardized ratio 1.8. Among agents used that cause DILI in this population the most frequent were antimicrobials (51%), cardiovascular agents (7%), antineoplastic agents (6%), and central nervous system agents (4.5%). (4)

As in the previously cited article, in this study the second most widely used class of drugs were cardiovascular (34.4%). As a class, angiotensin-converting enzyme inhibitors in patients with cirrhosis produce adverse effects mainly related to hyperkalemia and worsening of renal function. In the study by Franz et al. 19% of patients treated with an angiotensin converting enzyme inhibitor experienced adverse effects. In that same study, of the 146 patients taking beta-blockers, 7 patients suffered adverse effects. (23).

In our study, NSAID were used in 8.2% of patients. NSAIDs are a class of drugs largely used, often self-managed in the indications and dosages, not always requiring a medical prescription, leading to a high risk of adverse effects, including the risk of liver injury (30). NSAIDs should be avoided in cirrhotic patients, especially those with hydrosaline retention, because they inhibit the synthesis of renal prostaglandins (essential for the maintenance of decreased renal perfusion by activation of vasoconstrictor systems) and may precipitate functional renal failure. Since kidney failure can lead to fatal compliments in a cirrhotic patient, NSAIDs should not be the first choice in patients with ALF (30). An Italian multicenter study found that the annual incidence of DILI induced by NSAIDs was two cases per 100 000 inhabitants with odd rate of 1.69 [95% CI , 1.21–2.37], with nimesulide and ibuprofen associated to a statistically significant increased risk of liver damage, odd ratio of 2.10 (95% CI, 1.28–3.47) and 1.92 (95% CI, 1.13–3.26) respectively (31).

DILI can have several presentations from mild increase of liver enzymes to ALF and death (9). Chalasani et al. demonstrated higher mortality between patients with DILI and pre-existing liver disease vs healthy patients (16% vs 5.2%; P < 0.001) (4). In our study, 22% of patients died during hospitalization; of these, 28.4% used antibiotics (p <0.001), and 47.6% antifungal (p 0.004). DILI as a cause of ACLF represents 46.5% mortality (31). In our study 9 patients who had ACLF 6 died (66.7%), the age of these patients ranged between 51-70, being decompensation of cirrhosis the cause in 3 patients and infection in the others.
This study has certain strengths that must be emphasized: this is one of the few studies at national level where the prescription of hepatotoxic drugs in patients admitted to a tertiary hospital was evaluated. The results have shown that a large number of patients received potentially hepatotoxic drugs that could have been avoided. On the other hand, there are limitations: this is a retrospective study, it is not possible to safely infer the causal relationship between the drug used and laboratory changes and the presence of mortality, and there may be other confounding factors.

Attributing to the drugs the elevation in liver enzymes is misleading as in absence of a proper adjudication process, liver enzymes can be elevated in these patients because many other causes including infection, liver ischemia in the setting of bleeding or acute on chronic liver failure.

We did not always have access to some important data such as the reason for the indication of each drug, the latency time and its relationship with changes in the liver enzymes. Furthermore, ALT (≥5 ULN) or ALP (≥2 ULN) (with accompanying elevations in concentrations of GGT), were considered significant abnormalities without considering in patients with CLD what their previous baseline values were, so this could have overestimated the group of patients with altered liver enzymes.

Conclusion

The present study expands current knowledge of prescribing patterns for associated conditions in patients with underlying liver disease. Potential hepatotoxic drugs prescription is frequent in patients with CLD even in a tertiary university hospital, exposing these patients to additional risk. The risk for DILI development through the use of PHD in patients with liver disease is the subject of continuous controversy. In patients with liver disease, before prescribing any drugs it is crucial to assess the risk of DILI. Is essential to search for less hepatotoxic drugs, and when the potentially hepatotoxic medicine needs to be used, continuous laboratory monitoring is mandatory.
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List of abbreviations:
DILI, drug-induced liver injury
CLD, chronic liver disease
ALF, Acute liver failure
PHD, potentially hepatotoxic drugs
ACLF, acute-on-chronic liver failure
MELD, model for end-stage liver disease
GGT, gamma-glutamyl transferase
ALP, alkaline phosphatase
ALT, alanine aminotransferase
AST, aspartate aminotransferase
CI, confidence interval
NSAID, non-steroidal anti-inflammatory drugs
ULN, upper limit of normality

LATINDILIN, Latin American DILI Network

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Conflict of interest statement

The authors have nothing to disclose.

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