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Drug-induced liver injury causality assessment data from a cross-sectional study in Brazil: a call for the use of updated RUCAM in hospital pharmacy

Michele Müller LUNARDELLI[1], Matheus William BECKER[1], Gabriela Xavier ORTIZ[1], Carine Raquel BLATT[2]

[1]Graduate Program in Medicine – Hepatology. Federal University of Health Sciences of Porto Alegre, Porto Alegre, RS [2]Pharmacology Sciences Department, Graduate Program in Medicine – Hepatology. Federal University of Health Sciences of Porto Alegre, Porto Alegre, RS, Brazil

Corresponding author: Ortiz GX, gabrielax@ufcspa.edu.br

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Abstract

Objective: to identify the frequency of DILI inpatients from abnormal liver enzyme levels using the updated Roussel Uclaf Causality Assessment Method (RUCAM) causality assessment algorithm, as well as to provide a descriptive analysis of DILI cases. **Methods:** we conducted a cross-sectional study in a medium complexity hospital in southern Brazil. Data regarding DILI was collected retrospectively from electronic medical records (EMR) in 2015. Inclusion criteria were all adult patients (≥ 18 years old) who presented alanine aminotransferase (ALT) greater than twice the superior limit of normality (ALT > 60 UI/L) with concomitant change of aspartate aminotransferase (AST) or alkaline phosphatase (ALP) or change of ALP greater than twice the superior limit of normality (ALP > 250 UI/L) during hospitalization. The RUCAM was applied to all suspected DILI cases. **Results:** 84,134 inpatients in this period; 178 patients had abnormal liver tests, six patients had sufficient medical information to allow DILI causality assessment, and two patients had DILI described in EMR, although our group could not find sufficient information to apply RUCAM retrospectively. Absence of information was mainly related to drug reconciliation at hospital admission, time of onset of suspected drug therapy and no description of previous clinical conditions in EMR. Four patients developed hepatic injury as a result of drug treatment initiated during hospitalization. Suspected drugs were antibiotics, nonsteroidal anti-inflammatory drugs, antiviral, tuberculostatics and platelet antiaggregant. Liver injury pattern was identified as hepatocellular and mixed. **Conclusion:** DILI appeared as a rare ADR, but absence of data in most EMR affected the application of RUCAM and underestimated DILI frequency. There is an urgency to develop DILI knowledge in Brazilian hospitals. Pharmacists must be aware of the use of the updated RUCAM to prospectively assess possible DILI cases. For future research, we suggest to combine cross-linking DILI tracers such as ICD-10 liver injury codes, abnormal liver biomarkers, search for trigger hepatotoxicity drugs and EMR text search tools, adding artificial intelligence to pharmacovigilance and hospital pharmacy.

Key words: Chemical and Drug-Induced Liver Injury; Adverse Drug Reaction; Roussel Uclaf Causality Assessment Method; RUCAM; Hospital Pharmacy Service; Pharmacovigilance.

Dados da avaliação de causalidade de lesão hepática induzida por medicamentos de estudo transversal no Brasil: incentivo ao uso do RUCAM atualizado na farmácia hospitalar

Resumo

Objetivos: identificar a prevalência de pacientes internados com DILI por níveis anormais de enzimas hepáticas usando o algoritmo atualizado de avaliação de causalidade Roussel Uclaf Causality Assessment **Method** (RUCAM), bem como fornecer uma análise descritiva dos casos de DILI. Métodos: foi realizado um estudo transversal em um hospital de média complexidade do sul do Brasil. Os dados referentes a DILI foram coletados retrospectivamente de prontuários eletrônicos (EMR) em 2015. Os critérios de inclusão foram todos os pacientes adultos (≥ 18 anos) que apresentassem alanina aminotransferase (ALT) maior que duas vezes o limite superior da normalidade (ALT > 60UI/L) com alteração concomitante de aspartato aminotransferase (AST) ou fosfatase alcalina (ALP) ou alteração de ALP maior que duas vezes o limite superior da normalidade (ALP > 250 UI/L) durante a internação. O RUCAM foi aplicado a todos os casos suspeitos de DILI. **Resultados:** 84.134 pacientes internados neste período; 178 pacientes tinham testes hepáticos anormais, seis pacientes tinham informações médicas suficientes para permitir a avaliação de causalidade de DILI e dois pacientes tinham DILI descrito em EMR, embora nosso grupo não tenha encontrado informações suficientes para aplicar RUCAM retrospectivamente. A ausência de informações esteve relacionada principalmente à reconciliação medicamentosa na admissão hospitalar, tempo de início da suspeita de terapia medicamentosa e não descrição de condições clínicas prévias no EMR. Quatro pacientes desenvolveram lesão hepática como resultado do início do tratamento medicamentoso durante a internação. As drogas suspeitas foram antibióticos, anti-inflamatórios não esteroidais, antivirais,

tuberculostáticos e antiagregante plaquetário. O padrão de lesão hepática foi identificado como hepatocelular e misto. **Conclusão:** DILI apareceu como RAM rara, mas a ausência de dados na maioria dos EMR afetou a aplicação de RUCAM e subestimou a frequência de DILI. Há uma urgência em desenvolver o conhecimento DILI nos hospitais brasileiros. Os farmacêuticos devem estar cientes do uso do RUCAM atualizado para avaliar prospectivamente possíveis casos de DILI. Para pesquisas futuras, sugerimos combinar rastreadores DILI, como códigos de lesão hepática ICD-10, biomarcadores anormais de fígado, pesquisa de medicamentos de conhecida hepatotoxicidade e ferramentas de pesquisa de texto EMR, adicionando inteligência artificial a farmacovigilância e farmácia hospitalar.

Palavras-chave: Lesão hepática induzida por medicamentos; Reação Adversa a Medicamento; Roussel Uclaf Causality Assessment Method; RUCAM; Farmácia Hospitalar; Farmacovigilância.

Introduction

Drug therapy is widely used in health promotion, disease prevention and in diagnostic tests. However, it also presents the risk of adverse drug reactions (ADR) occurrence[1]. It is estimated that the median prevalence of ADR related to hospitalization in developed and developing countries are 6.3% and 5.5% respectively, and the median proportions of preventable ADR in developed and developing countries are 71.7 % and 59.6 % [2]. The frequency of ADR leading to hospital admissions is 6.5%[3] therefore, this is a major concern for patient safety and a burden for healthcare services as it may prolong hospital length of stay and costs [4,5].

Drug-induced liver injury (DILI) is a specific ADR that causes liver damage due to use of prescription or over-the-counter drugs, as well as herbal products. It is the leading cause of acute liver failure in the USA and the main responsible for US Food and Drug Administration (FDA) regulatory actions. The main signs and symptoms of DILI are fatigue, nausea, abdominal pain, immunoallergic signs, fever, rash, adenopathy and abnormal transaminase levels, leading to liver damage[6].

Drug-induced liver injury is categorized as acute or chronic and the injury pattern is hepatocellular, cholestatic or mixed, defined by the R value (the ratio of ALT and ALP expressed as multiples of the upper limit of normal). It is classified as intrinsic (predictable after excessive exposure to the drug), idiosyncratic (unpredictable and potentially serious due to user susceptibility factors) or "indirect" (unintentional injuries due to biological actions of a drug). Mechanisms of injury are related to serum levels of metabolites exceeding the upper limit of toxicity, drug inducing immune autoreactivity after liver metabolization, mitochondrial damage, hepatic steatosis or bile duct blockage. Onset of liver injury occurs days or weeks after drug discontinuation [7,8.] For example, cholestatic injury can happen within 90 days after medication use [8].

Drug-induced liver injury is responsible for fulminant hepatic failure in 13% to 30% of cases worldwide [9,10,11]. In a retrospective study, 35% of DILI confirmed cases developed acute liver failure (ALF) with death/transplant progression[12]. However, there is a very low sensitivity when searching for DILI in hospital databases using only the ALF descriptor without association with pharmacovigilance registers[13]. Also, confounding variables, misconceptions and absence of essential clinical information in Electronic Medical Records (EMR) may attribute ALF to DILI incorrectly. The Roussel Uclaf Causality Assessment Method (RUCAM) is underused in clinical practice and this may contribute to miss diagnosis and interpretation of many ALF cases regarding causality assessment (14). In addition, 50% of cases occurring in a hospital environment are poorly diagnosed when they appear in sectors where there is no follow-up by a hepatologist. Agile and efficient diagnosis can reverse patients' poor prognosis [15,16].

A systematic review of DILI cases in Brazil detected 27 studies reporting 32 cases. Brazilian cases were primarily identified in hospitals and occurred mainly in young male patients suffering from chronic diseases. Medicine use (n=29) was more frequent than herb use (n=3). Fifteen of the suspicious drugs appeared in the Brazilian List of Essential Medicines (RENAME) from 2018. In 50% of cases, clinical manifestations started within 30 days of drug ingestion. Although 50% of cases reached liver enzyme normality after drug withdrawal, seven deaths and two liver transplantations were reported [17].

The DILI is usually identified by establishing exposure time to the drug, development of signs and symptoms, alterations in liver tests and exclusion of other diseases such as infection, autoimmune diseases or other liver conditions[6]. The patient's improvement after drug discontinuation also reinforces the establishment of DILI diagnosis[7]. As there is no confirmatory laboratory test and it is mainly diagnosed by exclusion, identification of DILI is a challenge for healthcare professionals[8].

Research on ADR has mostly been restricted to analysis of spontaneous reports [18.] There is a wide variation in the prevalence of ADR-related hospitalizations among studies due to lack of gold standard tools for causality assessment, severity scaling, preventability classification, as well as healthcare professionals' knowledge about ADR, absence of electronic support and under-reporting practices 19, 20). Likewise, ADR reports related to hepatotoxicity are still sparse and subnotified, making it difficult to create guidelines to assist in the rapid prevention and identification of the occurrence of DILI in the Brazilian population [17].

In the pharmaceutical industry, preclinical phases of drug development are testing models based on chemical structures and molecular descriptors to predict DILI *;* [21]. In addition, new DILI biomarkers added to gene expression and genetic data are used to identify susceptible patients [22]. Clinical assessment of DILI may occur based on an expert medical opinion, but use of a quantitative scoring causality assessment method is strongly recommended. The use of the updated Roussel Uclaf Causality Assessment Method (RUCAM) algorithm is recommended by specialists to evaluate DILI, since it is the most reliable and reproducible validated method correlating liver damage to drug and herb use (23). Although RUCAM has been used worldwide for 25 years, only in 2020 it was validated for use in Brazilian Portuguese [24].

The RUCAM scale punctuates distinct domains such as liver injury pattern, timing of events, dechallenge, risk factors, comedications, alternative causes, known drug/herb hepatotoxicity and response to unintentional rechallenge[25]. It classifies liver injury as highly probable (≥ 9), probable (6-8), possible (3-5), unlikely (1-2) or excluded (≤ 0) in agreement to its likelihood of being DILI [8, 26]. Benefits of its use are the prospective assessment of cases, diverse application on epidemiological studies, case reports and clinical trials, satisfactory sensitivity and specificity with high positive and negative predictive values [25]. Drawbacks of the algorithm include

poor usability when missing information in retrospective cases, multiple drugs use, delayed DILI manifestation and subjective interpretation by the RUCAM applier [27]. Despite its limitations, RUCAM is the most recommended diagnostic tool for DILI [25].

Previous studies in Brazil evaluating DILI through international validated methods are recent, scarce and do not use standardized methodology, contributing to a healthcare scenario with questions to still be answered. The relevance of DILI study in the Brazilian hospital population, especially patients of medium to high complexity, often polymedicated, is of paramount importance, aligned with the World Health Organization precepts on health promotion and the Brazilian program of Patient Safety. We propose to identify the frequency of DILI by screening patients from abnormal liver enzyme levels using the updated RUCAM to provide epidemiological data and insights on the content and further guide pharmacovigilance actions and policies in hospital services.

Methods

A cross-sectional study was conducted in a medium complex hospital in Porto Alegre (RS), Brazil that has 200 hospitalization beds, an adult intensive care unit (ICU), surgical center and emergency service. Data were collected retrospectively from Tasy© EMR of patients in the period of January to December 2015. The EMR used provides information inserted by healthcare providers regarding a patient's health history, such as diagnoses, medicines, tests, allergies and treatment plan.

The inclusion criteria were all adult patients (≥ 18 years old) who during hospitalization presented ALT greater than twice the superior limit of normality (ALT > 60 UI/L) with concomitant change of AST or ALP or change of ALP to greater than twice the superior limit of normality (ALP > 250UI/L). Cases were excluded if there was no possibility of drug reaction due to no previous drug use and when the reason of hospitalization was clearly an alternative liver disease unrelated to DILI condition, evidently responsible for enzymatic changes of ALT, AST and ALP, such as cirrhosis, viral hepatitis, autoimmune hepatitis, alcoholic hepatitis, hepatic carcinoma and nonalcoholic fatty liver disease (NAFLD).

For all included patients, the following variables were analyzed: gender, age, history of previous diseases or current alternative diseases (sepsis, HBV, HAV, HCV, HEV and other hepatic diseases), habits (alcoholism), use of drugs with time frame between beginning and end of treatment, course of ALT during suspected medication use, other liver biomarker values of AST, ALP, bilirubin and international normalized ratio (INR), presence of imaging exams such as ultrasonography of the hepatobiliary pathways, computed tomography/ magnetic resonance cholangiopraphy and hepatotoxicity profile of prescribed medications. Liver injury pattern corresponded as follows: a) hepatocellular if R ≥5; b) mixed if >2 R <5; c) cholestatic if R ≤2 [7].

For suspected DILI cases, medication causality was retrospectively assessed through application of RUCAM by two trained experts [24]. If the case scored greater or equal to six, liver injury caused by drugs was probable or highly probable. The RUCAM analysis was made by two independent pharmacists (MJML and MWB). In case of disagreements, a third analysis of the case was made by CRB. For each case, EMR were checked if an explicit diagnosis of DILI by the medical team through the described classification of diseases (ICD) code was presented. Data were organized in a database with different classifications (variables) and analyzed through statistical analysis using the SPSS, version 23.

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations checklist was applied to this research to facilitate critical appraisal and interpretation of cross-sectional study results (28). According to ethical principles guiding research involving human beings, the project was submitted and approved by the Research Ethics Committee of Federal University of Health Sciences of Porto Alegre (UFCSPA) and is registered at the Brazil platform under number 56621616.0.0000.5345.

Results

In 2015, 84,134 patients were hospitalized among all services; 1,475 patients had elevated liver test results – ALT, AST or ALP and 220 of these matched the inclusion criteria of the study. We excluded 42 patients due to diagnosis of hepatic disease that was responsible for the variation of laboratory results of ALT, AST and ALP or no previous medication use- so DILI was immediately discharged. Therefore, 178 patients had abnormal liver tests that could be related to DILI and from this sample, only eight patients had sufficient medical information to allow DILI assessment.

The available information was insufficient for the application of RUCAM algorithm to 170 patients, preventing the definition of hepatotoxicity induced by drugs, as well as the elimination of such possibility. No description of the cause of liver injury by the physician was available in the EMR. Absence of information was mainly related to drug reconciliation in hospital admission, time frame of suspected drug therapy and no description of previous history of clinical conditions in EMR. Most of these patients entered the emergency service with abnormal liver tests and as soon as there was minimal recovery of the clinical condition, patients were discharged for ambulatory care. Furthermore, RUCAM establishes ALT follow-up for eight, 15 and 30 days after suspected drug discontinuation and in that scenario, it was not possible to make any correlation between DILI or other diseases.

Seven patients had DILI diagnosis described in EMR by physicians. After RUCAM algorithm application, two cases were assessed as possible, two as probable and two as highly probable. In two of these cases that DILI was described in EMR, our group could not find sufficient information to apply RUCAM retrospectively. One patient did not have explicit DILI description in EMR, but causality was assessed through the updated RUCAM as probable. In all cases, there was full recovery of hepatic function after suspected drug interruption, without adjuvant treatment. The average time from first abnormal transaminase serum level to normalization of hepatic function was six days.

Most patients in the DILI group were female (n=6) and the average age was 43,88 (±18,29), median was 39,5, ranging from 24 to 79 years-old, which did not differ statistically from the group without DILI. Four patients had current chronic diseases. In our study, four DILI cases (two of them due to over-the-counter drugs) primarily accessed the hospital through emergency service due to symptoms of hepatic injury. The other four confirmed cases developed hepatic injury as a result of drug treatment initiated during hospitalization with antimicrobials and antivirals.

Suspected drugs related to DILI were antibiotics (n=3; meropenem, clarithromycin and cefuroxime), nonsteroidal anti-inflammatory drugs (n=2; ibuprofen), antivirals (n=1; acyclovir), tuberculostatics (n=1; rifampicin + isoniazid + pyrazinamide + ethambutol) and

platelet antiaggregant (n=1; clopidogrel). Intoxication due to overdosage was excluded after prescription review of all eight cases. Considering our small sample, statistical analysis of independent variables (risk factors) of DILI was not performed.

Liver injury pattern was identified as hepatocellular (n=6) and mixed (n=2). The full description of cases is presented in Table 1 and the patient's RUCAM score for each domain is presented in Table 2. Transaminase serum levels from DILI patients varied from 73 IU/L to 1298 IU/L for ALT, from 41 IU/L to 1270 IU/L for AST, and from 147 IU/L to 202 IU/L for ALP. Clinically significant liver injury is defined as an AST level ≥5 × the upper limit of normal (ULN), ALT ≥5 × ULN, ALP ≥2 × ULN, total bilirubin ≥ 2.5 mg/dL or INR ≥ 1.5 (7).

Table 1. Description of confirmed drug induced liver injury cases detected from January to December 2015 in a general hospital.

Patient	Age (years)	Gender	Suspicious drug and dosage	Hospital sector	Time-to-onset (days)	Previous chronic disease existence	Clinical result after suspension of drug	Time frame between drug interruption and liver marker recovery (days)	Type of hepatic injury	Diagnosis of DILI	RUCAM algorithm
1	24	F	Ibuprofen 300mg, 6/6h (ambulatory use)	Emergency service	NI	No	Improvement of serum transaminases followed by hospital discharge	NI	Hepatocellular	Medical records by physicians	NA
2	39	M	Ibuprofen 300mg, 6/6h (ambulatory use)	Emergency service	7	No	Normalization of liver biomarkers and full recovery of hepatic function	7	Hepatocellular	No	Highly probable
3	26	F	RHZE (Rifampicin 150mg + Isoniazid 75mg+ Pyrazinamide 400mg + Ethambutol 275mg - pill) 4pills/day (ambulatory use)	Emergency service with subsequent admission	5	Tuberculosis	Improvement of serum transaminases followed by hospital discharge	NI	Hepatocellular	Medical records by physicians	Probable
4	40	F	Clopidogrel 75mg/day (ambulatory use)	Emergency service with subsequent admission	6	Ischemic cardiopathy	Normalization of liver biomarkers and full recovery of hepatic function	6	Hepatocellular	Medical records by physicians	Probable
5	48	F	Acyclovir 750mg, 8/8h (hospital use)	Emergency service with subsequent admission	5	Herpes zoster	Improvement of serum transaminases followed by hospital discharge	NI	Mixed	Medical records by physicians	Possible
6	35	F	Cefuroxime 1500mg, 8/8h (hospital use)	Emergency service with subsequent admission	NI	No	Improvement of serum transaminases followed by hospital discharge	NI	Hepatocellular	Medical records by physicians	NA
7	79	M	Meropenem 1000mg, 8/8h (hospital use)	Emergency service with subsequent admission	3	Hypothyroidism	Improvement of serum transaminases followed by hospital discharge	NI	Mixed	Medical records by physicians	Possible
8	60	F	Clarithromycin 500mg 12/12h (hospital use)	Emergency service with subsequent admission	5	No	Normalization of liver biomarkers and full recovery of hepatic function	5	Hepatocellular	Medical records by physicians	Highly probable

NI – No information in records; F- Female; M- Male; NA – It was not possible to apply the algorithm due to lack of information. Source: Prepared by the authors.

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Table 2. RUCAM score for DILI suspected cases

Patient	Drug	Item 1- Time to onset from the beginning of the drug/ herb	Item 1	Item 2 Course of ALT after after cessation of the drug/ herb	Item 2	Item 3 Risk Factor	Item 3	Item 4 - Concomitant drug/ herb use	Item 4	Item 5 Search for alternative causes	Item 5	Item 6- Previous hepatotoxicity of the drug/ herb	Item 6	Item 7- Response to intentional reexposure	Item 7	Total score	Causality
2	Ibuprofen	7 days	2	7 days	3	39 years-old non alcoholic	0	None	0	All causes group I and II reasonably excluded	2	Reaction labeled in the product characteristics	2	N/A	0	9	High probable
3	RHZE	5 days	2	N/A	0	26 years-old non alcoholic	0	None	0	All causes group I and II reasonably excluded	2	Reaction labeled in the product characteristics	2	N/A	0	6	Probable
4	Clopidogrel	6 days	2	6 days	3	40years-old non alcoholic	0	None	0	All causes group I and II reasonably excluded	2	Reaction labeled in the product characteristics	1	N/A	0	8	Probable
5	Acyclovir	5 days	2	N/A	0	48 years-old non alcoholic	0	None	0	The 7 causes of group I excluded	1	Reaction labeled in the product characteristics; Livertox score D	1	N/A	0	4	Possible
7	Meropenem	3 days	1	N/A	0	79 years-old non alcoholic	1	None	0	The 7 causes of group I excluded	1	Reaction labeled in the product characteristics; Livertox score D	1	N/A	0	4	Possible
8	Clarithromycin	5 days	2	5 days	3	60 years-old non alcoholic	1	None	0	All causes group I and II reasonably excluded	2	Reaction labeled in the product characteristics; Livertox score B	2	N/A	0	10	High probable

N/A- information not available; Group I causes: HAV, Hepatobiliary disorders, HCV, HEV, Alcoholism (AST/ALT ≥2), acute recent hypotension history (particularly underlying heart disease). Group II causes: complications of underlying diseases such as sepsis, metastatic malignancy, autoimmune hepatitis, chronic hepatitis B or C, primary biliary cholangitis or sclerosing cholangitis, genetic liver disease, citomegalovirus (CMV), EBV, HSV, VZV. LiverTox score definitions: A (well established cause of clinically apparent liver injury), B (highly likely cause of clinically apparent liver injury) and D (possible rare cause of clinically apparent liver injury); Source: prepared by authors based on the updated RUCAM checklist[8]

Discussion

DILI prevalence in the current study was approximately one case in 10,000 patients and none of our assessed cases was notified in the hospital pharmacovigilance system. Nonetheless, the low frequency observed has a potential bias due to the 170 missed cases with insufficient information. As most DILI studies are retrospective, it is estimated that approximately 60-70% of cases are not documented in EMR[16, 29]. Differences between DILI prevalence regarding study methodologies are considerable. In a French study, DILI was presented in 13.9 cases per 100,000 inhabitants or 16 times more frequent than the prevalence obtained through spontaneous reporting over the same time period (30). Herbal dietary supplement (HDS) and herbal medicines did not appear in 178 patients, differently from US DILI data which estimates increasing HDS as responsible for 20% of DILI cases in 2013-2014[7, 30]. This may occur because patients did not declare the herb use to their physicians, as it is not commonly seen as a drug with potential harm.

Among our 178 suspected cases of DILI, only six had sufficient data for RUCAM assessment causality. The absence of some information does not preclude the application of RUCAM, but entails a greater risk of bias as the lack of information lowers the case score and reduces the strength of correlation of the suspected drug with DILI [31]. The algorithm produces better results if it is prospectively applied, thereby assuring the integrity of data, impartial assessment by professionals and opportunity to collect relevant information while the patient is still under medical assistance [15, 25].

Drug-induced liver injury can cause liver necrosis, cholestasis, fatty liver, duct injury with significant bile duct loss and mixed immune inflammatory infiltrate[32]. Hepatocellular liver injury pattern was the most common (n=6), in accordance with previous studies [6, 7]. Hepatocellular DILI is more likely to be associated with poor outcomes and a higher liver-related mortality, and the type of liver injury will lead physicians to define treatment to be followed [30].

Drugs involved in the eight DILI cases are from a diverse pharmacological class such as antibiotics, anti-inflammatory agents, antivirals, tuberculostatics and platelet antiaggregants. Our findings corroborate the literature data, where the main responsible substances for the occurrence of DILI are: paracetamol,

amoxicillin/clavulanate, azithromycin, cefazolin, quinolones, tuberculostatics and antiretroviral agents (33). In an analysis of DILI in the American LiverTox® database of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the main classes of drugs involved were antimicrobials (33%), central nervous system drugs (12.5%), cardiovascular system (12.5%), rheumatology (12.5%), antineoplastics (10%) and endocrine (6%)[34].

Also, a review of worldwide data completeness and clinical quality of published idiosyncratic DILI cases established the main hepatotoxicity by drugs, from which rifampicin and ibuprofen appeared in our study[35]. Surprisingly, amoxicillin-clavulanate, which is the top one DILI causative drug, did not appear in our sample[35.] This medication is commonly used in community infections in ambulatory care through oral doses whereas in the hospital setting the choice is usually for intravenous broad-spectrum antimicrobials. In clinical practice, physicians should be aware of which drugs, herbs and complementary medicines are likely to cause DILI in their area, as it varies from geographical regions and products available[35].

Ibuprofen is an over-the-counter drug widely used by the Brazilian population through self-medication practices[36]. In an updated DILI systematic review[32], diclofenac was the most common causative nonsteroidal anti-inflammatory drug (NSAID) in the United States (63%) and Iceland (100%), while nimesulide frequently caused DILI in Latin America (38%) and Italy (39%). Ibuprofen was the NSAID responsible for most DILI cases in the Spanish DILI Registry (29%). Although NSAIDs hepatotoxicity is considered rare, ibuprofen is in the top 10 ranking of DILI drugs and as high dosages with long term use in self-medication commonly occurs in the Brazilian population, this information is an alert for intrinsic DILI occurrence [35, 37].

Oral anticoagulants (OAC) or antithrombotic agents are unlikely to be hepatotoxic. There are sparse case reports of OAC and DILI, including a signal for liver injury caused by rivaroxaban in the USA in 2015[38]. A population-based study in Iceland analyzed a ten-year period for OAC use and found three cases of DILI related to rivaroxaban[39]. Hepatocellular pattern of liver injury occurred with ALT/AST elevation. One patient used atorvastatin concomitantly, which has hepatotoxicity profile and could also be responsible for DILI. Our case with clopidogrel is probably related to idiosyncratic DILI due to patient characteristics.

Antimicrobials are protagonists in DILI case reports. In a prospective study conducted in the USA from 2004 to 2013, it was identified that among 899 cases of DILI, 36% were related to antibiotics, one of them specifically to meropenem[40]. Drug-induced liver injury caused by clarithromycin occurs in 3.8 in every 100 thousand patients with cholestatic pattern and slow manifestation of symptoms (three weeks) [42.] Only rare cases of DILI due to cefuroxime were published[40]. Acyclovir appeared in our study as a suspected drug. This antiviral is minimally metabolized by the liver and LiverTox© classifies this drug as a possible rare cause of clinically apparent liver injury [43]. Although antiretroviral therapy (ART) did not appear in our DILI study, it is noteworthy that ART such as efavirenz, nevirapine, abacavir and ritonavir are important DILI inducers leading to regimen/discontinuation of HIV therapy in 30% of patients (44). RHZE therapy (Rifampicin 150mg + Isoniazid 75mg + Pyrazinamide 400mg + Ethambutol 275mg) is used as first line treatment against tuberculosis and has potential to cause hepatocellular injury[45]. In Taiwan, 15.9% of patients had liver abnormalities after their tuberculosis (TB) treatment and the authors suggest close monitoring of liver functions in patients with pre-existing liver disease[46]. Another study suggested that patients should routinely have liver tests during tuberculosis treatment to capture early DILI[47].

The occurrence of DILI caused by TB and HIV treatment is a reality in Brazil. Becker et al. performed a review of Brazilian DILI cases evidencing that most Brazilian DILI investigations occur in specific populations, mainly HIV and TB. Besides the known hepatotoxicity profile of these drugs, this population has well-structured ambulatory follow-up by their infectologists provided by the National Health Service (Brazilian SUS - Sistema Único de Saúde), as well as clinical guidelines suggesting the need of liver function attention[48]. Hospital services should closely monitor patients who use treatments containing drugs with potential for hepatotoxicity that may worsen clinical outcomes.

Some risk factors are associated to DILI such as age >55 years old, female sex, alcohol consumption, previous liver disease, immune dysfunction, chronic diseases such as diabetes and hypertension, gestation, among others[30,48]. The frequency of DILI will vary according to patient profile and drug use. Clinical pharmacists who monitor adverse drug reactions in hospitals should pay special attention to patients who may present all these risk factors associated with a prescription of hepatotoxic drugs to promote patient safety actions. In addition, benefits and harms of continuing the suspected DILI drug may be balanced by the medical staff, although interrupting the causative agent is proved to be substantial for clinical improvement, preventing the chance of serious liver damage[7, 30.]

Idiosyncratic is the most common type of DILI when excluding ALF due to paracetamol overdosage (intrinsic). It is also the most challenging liver disorder for hepatologists due to its variety of clinical pathological mechanisms and absence of specific biomarkers [33]. Laboratory data has been utilized in the detection algorithm for DILI alongside International Classification of Diseases (ICD-10) codes in EMR in most retrospective studies[49, 50.] However, in our study, liver biomarkers by themselves were not enough to provide positive predictive values of DILI and performed mainly as trigger alerts. Algorithms for retrospectively DILI tracing should be developed, cross-linking liver injury ICD-10 codes, abnormal liver biomarkers and trigger hepatotoxicity drugs, and searching text tools in EMR to achieve better outcomes with less bias [29, 49, 50.]

LiverTox© is currently under discussion in the literature regarding the quality of its clinical evidence35. Many case reports graded the likelihood of a potential hepatotoxicity drug in LiverTox© without using RUCAM to assess causality and were based on expert medical opinion/ global introspection, general adverse drug reaction causality tools or even summing up the number of case reports of a specific drug, besides the presence of no updated information[51]. This situation contributes to misinformation and wrong likelihood association, misleading the scientific community. To overcome those gaps, transparent standard evidence-based features must appear in the LiverTox© analysis, and the database must encourage case reports with updated RUCAM causality application [51].

Publications on DILI must explore and apply the updated RUCAM prospectively. This is a major call to improve the quality of DILI knowledge, especially among healthcare professionals, as we have seen in our study the bias that not using a strongly validated method to assess DILI can cause. Hospital pharmacists must be aware of the use of the updated RUCAM to prospectively assess possible DILI cases. After our study, we expect that in the future, even in cases where the EMR does not have all the information, it will be possible for the hospital pharmacist to contact practitioners and inpatients for missing clinical relevant information in order to contribute to the diagnosis and adequate clinical management of the inpatient. Pharmacists have co-responsibility to include clinical data in the EMR.

This study presents all the limitations of a retrospective study design. Potential sources of bias are the lack of relevant clinical information in EMR that could change the prevalence of DILI in the sample. Furthermore, this study presents a small and non-homogenous sample that could not be used to extrapolate findings to the Brazilian population (generalizability) or analyze risk factors associated with DILI. Finally, although transaminases per se are not enough to predict DILI, liver biomarkers allied to RUCAM analysis are important tracers for clinical DILI relevant cases even when retrospectively applied. Despite limitations, we believe relevant data regarding DILI applied to the Brazilian health context were brought to light and may help healthcare professionals in this field to overcome current gaps in patient safety and DILI.

Conclusion

The detection of DILI cases with retrospective data from patients with liver enzyme abnormalities resulted in a ratio of 1 DILI case for every 10,000 patients. All cases of DILI had positive outcomes. However, better results to identify DILI can be obtained from the prospective follow-up of suspected cases with alterations in liver enzymes.

DILI evidence is mainly built on retrospective data and spontaneous reports. As a result, there is an important risk of bias due to lack of medical information and data completeness. We conclude that although RUCAM has many limitations when applied retrospectively, it is still the best tool currently available in the international literature for assessing the causality of liver injury. One must be aware that there is an urgency for prospective study designs to evaluate Brazilian DILI epidemiological data and to reassess the hepatotoxicity profile of drugs, as well as with prospective use of the updated RUCAM, timely collecting case data in order to get complete data for high causality gradings. To this end, the participation of hospital pharmacists is essential. Pharmacists are the main professionals to provide support in reducing ADR damage to patients.

The proper insertion of relevant clinical information in medical records of hospitals is a challenge worldwide and except for specific monitored patients using HIV and TB treatments, there is a poor effort to identify and report DILI cases. Health education may be the pathway to disseminate DILI knowledge regarding hepatotoxicity and how to assess it.

Algorithms for DILI tracing should be developed using computer systems and machine learning to identify possible DILI cases. We suggest cross-linking DILI tracers such as liver injury ICD-10 codes, abnormal liver tests, drugs that cause hepatotoxicity and searching text tools in EMR. This scenario would be helpful for hospitals with proper infrastructures, but we understand this may not be the majority of Brazilian hospitals. The updated RUCAM is a critical tool for assessment of DILI causality by hospital pharmacists and its knowledge and application should be disclosed in hospital pharmacy.

Conflicts of interest statement

The authors declare no conflict of interest.

Collaborators

MJML and MWB collected the data and wrote the paper; CRB wrote and revised the paper; GX performed the final review of the manuscript with significant contributions; all authors approved the final version of the manuscript.

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