Drug induced liver damage in a university hospital

Lesão hepática induzida por drogas em um hospital universitário

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INTRODUCTION

Drug induced liver injury (DILI) is a great problem of public health. It is the first cause of acute liver failure, being responsible for a broad spectrum of liver diseases. It is a challenge to pharmaceutical industry, requiring studies with a big number of patients to study the drug safety. Hepatotoxicity may be caused by a direct liver injury or a dysfunction developing cellular lesion. Peroxidation of lipids in hepatocytes membrane by free radicals or intermediary metabolites is an example of direct mechanism. Other mechanisms are covalent bound with intracellular proteins, apoptosis activation, mitochondrial inhibition and interference with proteins involved in biliary salt exportation, or immunologic mechanisms, with the destruction of hepatocytes by a cytokine Tumor Necrosis Factor: TNF and/or Fas. Herbal and Dietary supplement (HDS) were responsible for 43% of the DILI cases in some studies. In a reference center in USA, drug induced hepatotoxicity was cause for 32 of 96 (33%) fulminant hepatitis cases. Another study, on Massachusetts general population, showed a 40,6/100.000 persons for year incidence of hepatotoxicity causing liver enzymes anormality.

CONCLUSION: DILI is caused by a wide variety of drugs, dietary supplements and dietary supplements. Anti-infectives and chemotherapy were responsible for much of the response.

Keywords: Herbal and dietary supplements. Toxic Hepatitis. Drug-Induced Liver Injury.
were: acetaminophen (17%), antiretroviral therapy (17%), chemotherapy, including flutamide, cyclophosphamide, methotrexate, methotrexate and cytarabine, (12%), anticonvulsants (10%), antibiotics (9%), diclofenac (9%), anesthetic agents (5%), antitubercular agents (3%). The aim of this study was identify and characterize cases of hepatotoxicity induced by drugs, herbal and dietary supplements in an University Hospital in Brazil.

RESULTS

From August 2009 to September 2014, 30 patients were included, 50% (16/30) were female, mean age of 39 years; 77% (23/30) individuals were afrodescendant. Of total of patients 30, 23% (7/30) presented at least one of the following symptoms: abdominal pain, jaundice, choloria or pruritus. There were no patients with fever, arthralgia, rash or eosinophilia. Only one patient with previous cirrhosis developed hepatic encephalopathy.

The R value was calculated from the lab values results on the day of DILI recognition. Cholestatic or mixed injury pattern were present in 73% of patients and 27% (8/30) had hepatocellular pattern injury.

DILI was caused by allopathic medicine in 90% (27/30), by HDS in 6% (2/30) and 4% (1/30) recreational drug. The most implicated drugs were: antituberculostatics 23% (7/30), anti infection 17% (5/30), antineoplastic 14% (4/30). Non-steroidal anti-inflammatory drugs 6% (2/30), oral contraceptive 6% (2/30) and immunosuppressant 6% (2/30) (Figure 1).

Figure 1 – Frequency of drugs causing DILI cases in Universitary Hospital of 2009 at 2012.

The allopathic medicine most frequent was isoniazid, HDS and recreational drug found were an infusion tea “mãe boa” – Ruellia baiensis, RIP CUTZ® (3 2-c pyrazole – 5alpha – etioallocholane-17b – tetrahydropryranol 16,6mg, 2a, 17a dimethyl-eti ocholan-3-one, 17b-ol 10mg e 2a, 3a ethipho-17a-methyl-17b-hydroxy-5a-androstan 5mg) – anabolic steroid; and “crazy princess”– a Berber mix of brandy, sugar-cane liquor, vodka, Erythroxylum catuaba, honey, Paulinia cupana, Zingiber officinale and Allium sativum.

Complete remission was observed in 70% (21/30) of the cases after suspended the related drug, 27% (8/30) needed treatment and in 3% of (1/30) cases had liver transplant. None patient performed rechallenge. All the patients had complete recuperation None of patients developed chronic DILI, and 1 patient progressed to acute liver failure.

By using the CIOMS for drug causality assessment, 60% (18/30) were classified as highly probable, 27% (8/30) as probable and 23% (5/30) were as possible.
DISCUSSION

DILI is one of the most common type of liver disease in hepatology. In this study 51% of the patients were female, and the average was 38 years (20 to 64 years). This data was similar with the previous literature related, such as Andrade et al., in a multicentric study from Spain (461 patients in a 10 year period). Sgro et al., in a 34 cases study with french population15 and Chalasani13, who studied 300 patients in United States14, founded the same results.

The anti-infections drugs as (isoniazid, voriconazole, amphotericin, abacavir, nevirapin, meglumine antimoniote and ciprofloxacin) share the majority of reactions, 41% of cases. Antineoplastic agents (melphalan, etoposide, dasatinibie, cyclosporine e imatinibie) were second culprit drug most common in these cases. Chalasani et al., stated that in 217 patients who had only one drug involved in the hepatic injury, the most therapeutic class was anti-infectives and central nervous system drugs13. In Spain, in a 10-years of DILI registry, the main pharmacological groups were anti-infectives drugs, central nervous system and non-steroidal anti-inflammatory drugs12.

The anabolic steroid and homemade infusions was observed too. In Iceland 16% of the DILI, was associated with herbal supplies. In recent Spanish Study, DILI was related in 2,3% of the patients using Anabolic Steroids drugs, we found similar data in this study19. According to Andrade et al, DILIN secondary to anabolic steroid drug had increased reports from 7% to 20 % between 2004 at 201321. In this study 3% of the reported cases was HDS. The herbal medicines implicated with the liver damage were Ruellia baiensis, Erythroxylum catuaba, Paullinia cupana, Zingiber officinale and Allium sativum. In this herbal species, was reported DILI with Paullinia cupana, one case and Paullinia cupana, two cases, the others species weren’t report in literature14,15.

In a series of 34 DILI cases, Sgro et al. found 10% of non-steroidal anti-inflammatory drugs16, and in the Spanish registry was related, along 10-years, 11% of DILI cases was non-steroidal anti-inflammatory drugs. The frequency this drug in our studied population was less when, only 6%, but our patient sample was smaller when compared that Spanish Group13.

In this study, 72% of DILI had cholestatic or mixed injury pattern. Sgro et al. and Chalasani et al. also showed difference in frequency between fenotipe of liver injury11,18. However, among patients who had acute liver failure, Chalasani et al. found 82% of the lesions with hepatocellular injury, data corroborated by Reuben et al., where 71% of acute hepatic failure by DILI were with hepatocellular pattern14,17. The only case that occurred with acute liver failure, probably secondary to herbal medicine, Ruellia baiensis, also had hepatocellular damage.

In this series, isoniazid was the substance that appeared most frequently involved in the etiology of the hepatic injury. Andrade et al. and Chalasani et al. found amoxicillin – clavulanate as the most common individual agent in the causes of DILI11,12. In our study there were no registered cases.

In relation to severity one only patient had acute liver failure, and recovered with liver transplant. Application of CIOMS/RUCAM scale produced as highly probable in 60% of these cases in the study. In others studies, RUCAM scale showed as probable in the majority of the studies13.

CONCLUSION

This is the first DILI cases reported in our hospital population. In this study anti-infective drugs and chemotherapy drugs were responsible for the most of hepatic injury. Hepatocellular damage was the most common phenotype of DILI in this sample and the most of patients had completely recuperation.

REFERENCES

1. BITTENCOURT, P. Epidemiologia da hepatotoxicidade por drogas. In: Reunião com Expertos em Hepatotoxicidade da Sociedade Brasileira de Hepatologia: analgésicos, antitérmicos, insumos vegetais, fitoterápicos, homeopáticos e AINES. GED Gastroenterol. Endosc. Dig., São Paulo, v. 30, n. 1, p. 14-16, 2011.
2. DUH, M. S.; WALKER; A. M.; KRONLUND JUNIOR, K. H. Descriptive epidemiology of acute liver enzyme abnormalities in the general population of central Massachusetts. Pharmacopédiomol. Drug Saf., Chichester, v. 8, n. 4, p. 275-283,1999.
3. BERTOMLAMI, M. C. Mechanisms of hepatotoxicity. Arq. Bras. Cardiol., São Paulo, v. 85, n. 5, p. 25-27, 2005.
4. VEGA, M. et al. The Incidence of Drug – and Herbal and Dietary Supplement-Induced Liver Injury: Preliminary Findings from Gastroenterologist-Based Surveillance in the Population of the State of Delaware. Drug Saf., Auckland, v. 40, n. 9, p. 783-787, 2017.
5. PARANÁ, R.; WASKMAN, J. C. Mecanismos de hepatotoxicidade medicamentosa: o exemplo do acetaminofén/paracetamol. In: Reunião com Expertos em Hepatotoxicidade da Sociedade Brasileira de Hepatologia: analgésicos, antitérmicos, insumos vegetais, fitoterápicos, homeopáticos e AINES. GED Gastroenterol. Endosc. Dig., São Paulo, v. 30, n. 1, p. 10 – 13, 2011.
6. TAJIRI, K.; SHIMIZU, Y. Practical guidelines for the diagnosis and early management of drug-induced liver injury. World J. Gastroenterol., Beijing, v. 14, n. 44, p. 6774-6785, 2008.
7. U.S. National Library of Medicine. Causality. Bethesda. Disponível em: <https://livertox.nih.gov/>. Acesso em: 15 apr. 2016.
8. U.S. National Library of Medicine. Glossary. Bethesda. Disponível em: <https://livertox.nih.gov/>. Acesso em: 15 apr. 2016.
9. AITHAL, G. P. et al. Case definition and phenotype standardization in drug-induced liver injury. Clin. Pharmacol. Ther., St. Louis, v. 89, n. 6, p. 806-815, 2011.
10. BENICHOU, C. I.; DANAN, G.; FLAHULT, A. Causality assessment of adverse reactions to drugs—II. An original model for validation of drug causality assessment methods: case reports with positive rechallenge. J. Clin. Epidemiol., Oxford, v. 46, n. 11, p. 1331-1336, 1993.
11. CHALASANI, N. et al. Causes, Clinical Features, and Outcomes From a Prospective Study as Drug-Induced Liver Injury in the United States. Gastroenterology, Baltimore, v. 135, n. 6, p. 1924-1934e4, 2008.
12. ANDRADE, R. J. et al. Drug-Induced liver injury: a analysis of 461 incidences submitted to the spanish registry over a 10-year period. Gastroenterology, Baltimore, v. 129, n. 2, p. 512-521, 2005.

13. MEDINA-CALIZ, I. et al. Herbal and dietary supplement-induced liver injuries in the spanish dili registry. Clin. Gastroenterol. Hepatol., Philadelphia, v. 16, n. 9, p. 1495-1502, 2018.

14. SCHÖPFER, A. M. 1. et al. Herbal does not mean innocuous: ten cases of severe hepatotoxicity associated with dietary supplements from Herbalife products. J. Hepatol., Amsterdam, v. 47, n. 4, p. 521-526, 2007.

15. TESCHKE, R. 1. et al. Herbal hepatotoxicity: a tabular compilation of reported cases. Liver Int., Oxford, v. 32, n. 10, p. 1543-1556, 2012.

16. SGRO, C. et al. Incidence of Drug-Induced Hepatic Injuries: A French Population-Based Study. Hepatology, Baltimore, v. 36, n. 2, p. 451-455, 2002.

17. REUBEN, A.; KOCH, D. G.; LEE, W. M. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology, Baltimore, v. 52, n. 6, p. 2065-2076, 2010.

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