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Case Report

Multiple Drug-Induced Liver Injury: Case Report

*Ahmed Zaiem**

Department of Pharmacology, University of Tunis-El Manar, Faculty of Medicine & Pharmacovigilance Center of Tunisia, Tunisia

Abstract

Drug-Induced Liver Injury (DILI) is a leading cause of acute liver failure and represents the first cause of fatalities related to Susceptibility to DILI is believed to be the consequence of the drugs interplay of multiple factors, and it is currently not feasible to predict its occurrence in patients who have already suffered an episode. Recurrent DILI with different drugs of drug-induced hepatotoxicity is exceptional even among drugs that share similar chemical structures. We report an exceptional case of a woman who presented recurrent DILI caused by structurally unrelated drugs. The case was notified to the Tunisian national centre of pharmacovigilance on November 13th 2017.

Case Presentation

A 45-year-old woman, with a medical history of cholecystectomy, received piroxicam, cotrimoxazole, omeprazole and metoclopramide for gastrointestinal trouble on July 2013. The patient had no history of alcohol use or recent transfusion of blood product. She had no known autoimmune disease, cardiac or endocrine pathology. Three days after starting this therapy, she developed conjunctival jaundice, dark urine and clay-colored stools. Laboratory testing showed Alanine Aminotransferase (ALT) 215 IU/L, Aspartate Aminotransferase (AST) 132 IU/L, Alkaline Phosphatase (ALP) 783 IU/L, total bilirubin 11.2 mg/dl, leucocyte count 11.3 x 109 with eosinophils 120 and prothrombin index 0.97. Serological tests for hepatitis A, B, C and E were negative: anti-HAV-IgM, HBs-Ag, Anti-HBc-IgM, HBe-Ag, anti-HCV, anti-HEV-IgM, anti-HEV-Ig G. The PCR was also negative: HBV-DNA, HCV-RNA, HEV-RNA. Serological tests for CMV, EBV, HSV and VZV were negative (IgM and IgG). Auto-antibodies Antinuclear Antibodies (ANA), Smooth Muscle Antibodies (SMA), Anti-Mitochondrial Antibodies (AMA), Anti-Smooth Muscle Antibodies (ASMA), anti-Liver-Kidney Microsomal Antibodies (anti-LKM) and Peripheral Anti-Neutrophil Cytoplasmic Antigen (pANCA) were normal. Ultrasonographic examination showed a normal biliary tract. Magnetic Resonance Imaging (MRI) of biliary ducts was normal. One month after drug cessation, the clinical manifestations disappeared and patient's laboratory tests improved completely. On August 2017, the patient took mefenamic acid for pharyngitis. Two days later, she presented jaundice and darkening of urine. Laboratory testing revealed elevated liver enzymes AST 252 IU/L, ALT 292 IU/L, total bilirubin 13.5 mg/dL, ALP of 348 IU/dL, Gamma Glutamyl-Transpeptidase (GGT) 130IU/dL. Prothrombin activity was normal. Ultrasonographic examination showed a normal biliary tract. Serological tests for hepatitis A, B, C and E were controlled and were negative. The PCR was also negative: HBV-DNA, HCV-RNA, HEV-RNA. Serological tests for CMV, EBV, HSV and VZV were negative (IgM and IgG). The patient refused the liver biopsy. Discontinuation of this drug lead to the normalisation of hepatic enzyme levels after three weeks. The patient reported three other similar liver injuries associated once with the association spiramycin-metronidazole, a second time with lidocaine injected locally for dental care, and finally with paracetamol taken for headache. She had developed each time jaundice and darkening of urine. This was confirmed by her physician but unfortunately no details of these episodes were recorded (no laboratory testing available). The episodes resolved after drug withdrawal. Apart from these episodes associated with medication, the patient did not report the occurrence of jaundice or dark urine.

Discussion

This patient presented five different episodes of DILI with different drug classes having no common structures. Explorations for non-drug aetiology were all negative:, immunological assessment [1-5] extensive viral serology as recommended and radiography. Only the liver biopsy was not performed because of the patient's refusal. The episode of DILI which occurred in July 2013was attributed to drugs with a French causality assessment score of I5 for the four drugs (they had same chronology and the hepatotoxicity was. Therefore, we could label in the four products characteristics) not decide between these four drugs. The episode which occurred in August 2017was attributed to mefenamic acid with causality assessment score. For the remaining 3 episodes of DILI, because of the lack of [6] of I5 data concerning mainly chronology and laboratory testing, the causality assessment score cannot be rated. In the literature, adverse drug reaction to three or more drugs is defined as multiple drug intolerance. Multiple Syndrome (MDIS) [7], and only few cases were reported to date DILI is very uncommon. After a Medline search, we found only cases of patients developing recurrent DILI with only two different drugs This is to our knowledge the first case of recurrent DILI caused by more than two structurally unrelated drugs. Susceptibility to DILI is believed to be the consequence of the interplay of multiple factors, including those related to the structure of the drug, the patient's genetic background and the influence of underlying diseases and. The vast majority of DILI cases cannot be associated medications foreseen and are, therefore, termed idiosyncratic. Oxidative stress, reactive metabolites, mitochondrial toxicity, modulation of drug metabolizing transporters, induction of apoptosis or necrosis, as well

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***Corresponding author:** Ahmed Zaiem, Department of Pharmacology, University of Tunis-El Manar, Faculty of Medicine & Pharmacovigilance Center of Tunisia, E-mail: ahmed.zaiem@rns.tn; ahmed207@rns.tn

as immunoallergic reactions to protein adducts may all be involved in DILI, but for most of the drugs the specific mechanisms contributing to DILI are unknown [8]. Thus, trying to explain the mechanism of occurrence of multiple DILI to different drugs is even more difficult and complicated. Two possible mechanism were proposed by Lucena to one explain how a patient might develop DILI from different drugs possibility is that the mechanism is immune-mediated and the drugs or metabolites may share sufficient similarity to provide immunological cross-sensitization. This possibility may be valid in case of developing DILI from two different drugs, even three. In our case, this mechanism seems to be less probable since the recurrence of DILI five times with more than five different drugs. There were not found eosinophilia nor positivity in the immunological tests. An auto-immune hepatitis induced by drugs is discarded. A second hypothesis proposed by Lucena is that the culprit drugs share a common target and DILI is directly related to the case of DILI induced the pharmacological action of these drugs by structurally unrelated antibiotics raises the possibility of the existence of a common mechanism of liver injury for both drugs. This mechanism could hardly explain the occurrence of the five episodes of DILI in our patient since the absence of common pharmacological action of the drugs.

Conclusion

This observation reported an exceptional case of recurrent DILI caused by structurally unrelated drugs. The exact mechanism of such reaction is unknown. Physicians should be aware when prescribing medication in such patients since the reaction is unpredictable and can be even serious. Systematic monitoring of liver tests in these patients is recommended.

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