HEPATOTOXICITY OF ANTIBIOTICS IN DIFFERENT AGE GROUPS

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Abstract

Drug-induced liver injury (DILI), also referred to as drug - induced hepatotoxicity, constitutes a major clinical problem, which has become the leading cause of acute liver failure. This research aims to identify the main antibiotics that can cause liver damage and discuss their presentation, type and consequences including frequency and severity. Hepatotoxicity caused by antibiotics is usually asymptomatic, reversible, associated with only mild liver damage. However, in rare cases, the need for liver transplantation and death from acute liver failure have been reported. Hepatotoxicity is an uncommon adverse effect of the drug and the main cause of drug discontinuation. Most patients with liver injury associated with use of antibiotics have a favorable prognosis. However, patients with jaundice have approximately 10% risk of death from liver failure and/or require liver transplantation. In this regard, it is essential that doctors and patients are aware of and monitor possible symptoms for early detection of hepatotoxicity.

Keywords: Drug Induced Liver Injury (DILI), Antibiotics, Hepatotoxicity.

Introduction

During the last decade, liver toxicity has been one of the most frequent reasons for pharmacovigilance safety reports and withdrawal from the market of an approved drug. The liver is a major organ involved in the detoxification and secretion of many endogenous and exogenous substances. Liver dysfunction challenges not only healthcare professionals, but also pharmaceutical industries and drug regulatory agencies. Drug-induced liver injury (DILI), also referred to as drug-induced hepatotoxicity, constitutes a major clinical problem, which has become the leading cause of acute liver failure. Drug-induced **hepatotoxicity is one of the leading causes of acute and chronic liver disease and is also the most common side effect that halts the development of a new drug or leads to the withdrawal of approved drugs from the market (**Dass E. 2020) . **According to World Health Organization (WHO) statistics, DILI is ranked as the 5th leading cause of death worldwide (**Lu RJ, Zhang, et al 2016). **Maintaining a healthy liver is vital to the overall health of human beings. The liver is the largest and most complex internal organ of living systems, involved in the intermediary metabolism of proteins, fats and carbohydrates, acts as a storehouse of protein, glycogen, vitamins (**Das A., Biswas P. et al 2011). **Most drugs must pass through the liver, as it is the main site for their metabolism. Since in the liver, enzymes convert prodrugs to active metabolites or convert active drugs to inactive forms, the liver's primary mechanism for metabolizing drugs is via cytochrome P-450. However, the process is slower in some people and in these people there is a risk of liver damage. Hepatotoxicity is defined as liver damage or impairment of liver function caused by drugs or other non-pharmacological agents. (**Paniagua, **et al 2017). Many drugs can cause liver damage, but people react differently to different drugs. Some people may have an adverse reaction to certain drugs and may experience liver damage, while others may not. In rare cases, hepatoxicity can lead to chronic damage and bile duct obliteration syndrome (**Einar S. Björnsson. 2017)**. Antibiotics are considered the most common causes of hepatotoxicity.Antibiotic-induced hepatotoxicity is usually asymptomatic, transient, and associated with only mild liver damage. However, serious injury requiring liver transplantation has been reported in some cases (**Andrade RJ,.**2011) Hepatocytes,**

cholangiocytes, Kupffer cells, ductal and endothelial cells are involved in the mechanisms by which drugs cause hepatotoxicity that have direct effects on cellular organelles such as mitochondria, endoplasmic reticulum, or nucleus. Drug metabolites generated in the liver through biotransformation can cause liver damage due to the formation of toxic or reactive substances such as free radicals and thus a breakdown of a variety of chemical reactions can occur. These mechanisms can generate necrosis, apoptosis, or both (Paniagua et al **2017)**. Various environmental factors including age, gender, alcohol consumption, comorbidities and genetic factors are involved in each step and the degree of liver damage is different. If liver damage heals within 6 months, it is known as acute liver damage and if it persists for more than 6 months, it is known as chronic liver damage (Jeong III Suh, 2020). Chronic drug-induced liver injury defined as DILI with persistent liver injury is a global challenge with major difficulties in determining the cause and establishing effective treatment. Hepatotoxicity may be considered chronic when liver enzymes do not return to normal or baseline values after drug withdrawal and/or signs and symptoms of liver disease persist six months after the onset of DILI. Risk factors are important and may be useful for early detection of chronic liver damage. Elderly patients may be considered a risk factor due to reduced metabolic function. Chronic damage manifests as persistent inflammation of the bile ducts that progresses to cirrhosis and eventually requires a liver transplant. However, research on chronic DILI over the past decades is still lacking, and the incidence, phenotypes, mechanisms, risk factors, and treatment are not fully understood (Qiaoling Wang 2021). Drug-induced liver damage is usually reversible and is considered benign and improves after the drug is withdrawn. However, it sometimes progresses to liver failure, requiring a liver transplant or causing death. It is important to recognize and remove the suspected agent as soon as possible to prevent progression to chronic liver disease and/or fulminant hepatic failure (Stefan David 2010). Drug-induced liver damage presents a challenge to the clinician and hepatologist David E. Kleiner (2014).. Clinical features are an important basis for the diagnosis of drug-induced liver diseases. Since there are no specific diagnostic tests or specific biomarkers for idiosyncratic hepatotoxicity, its diagnosis is made after strictly excluding other causes of liver disease, evaluating the temporal relationship between drug use, abnormal liver tests, and evaluating improvement in liver tests after drug withdrawal. Hepatotoxicity caused by antibiotics can often be detected early by elevations of liver enzymes, Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Alkaline phosphatase (ALP), Gamma glutamyl transpeptidase (GGT) (Andrade RJ, 2011 ; Singh A, Bhat TK, Sharma OP. 2011; Stefan David 2010). The main aim of the study is to identify antibiotics that can cause hepatotoxicity and to highlight this side effect of widely used antibiotics, their frequency and severity.

Materials and methods

In order to realize the purpose and objectives of the study, the analysis-causal method was selected where all the specific elements of the study are presented, starting from the type of data, the cases analyzed and the development of the topic based on the general and specific objectives using the histories of the patients' illnesses from the mother doctors.In this study, a total of 29 patients of different genders and age groups from the Center for Family Medicine - Clinical Hospital of Tetova - of the Pollog Region were analyzed. Outpatients who were prescribed antibiotics for the treatment of bacterial infections by their primary care physician were analyzed, as well as hospitalized patients who were treated with antibiotics for various diagnoses. Carefully following the patient's history, the therapy he uses, the duration of antibiotic use, the time of their initiation and cessation. Biochemical data analyzed from (patient history): alanine aminotransferase (ALT), aspartate aminotransferase (AST), gammaglutamyl transpeptidase (GGT) and alkaline phosphatase (ALP) levels. The study was

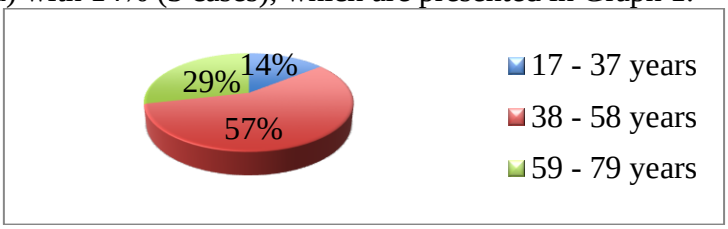
conducted according to a protocol designed in accordance with the ethical principles of the Declaration of Helsinki for medical research involving humans. Patients were informed in advance about the purpose of the study, about privacy, assuring them that the data collected from them would be anonymous and would not be identifiable (World Medical Association , 2001).

Statistical data processing

The results were processed and presented in tabular and graphical form using Microsoft Office Excel 2007.

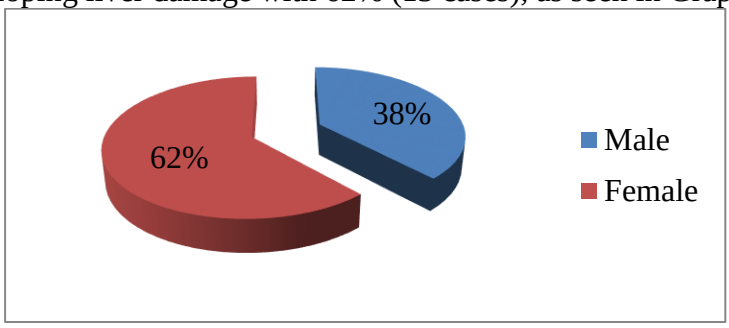
Results and discussion

This study analyzed a total of 29 patients of different age groups. In continuous follow-up of liver enzymes, only 21 patients resulted in hepatotoxic effects and only the results of patients in whom increased liver enzyme values were detected are presented below.
Of the cases included in the study, the most affected is age group II (38 - 58 years old) with 57% (12 cases), followed by age group III (59 - 79 years old) with 29% (6 cases) and age group I (17 - 37 years old) with 14% (3 cases), which are presented in Graph 1.



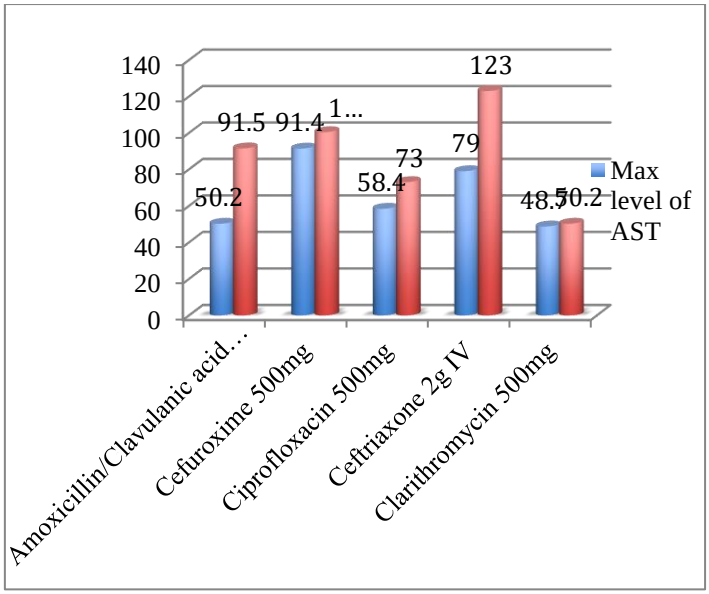
Graph 1. Incidence of hepatotoxicity according to age groups

Overall, compared to male patients comprising 38% (8 cases), female patients are at greater risk of developing liver damage with 62% (13 cases), as seen in Graph 2.



Graph 2. Susceptibility to hepatotoxicity according to gender

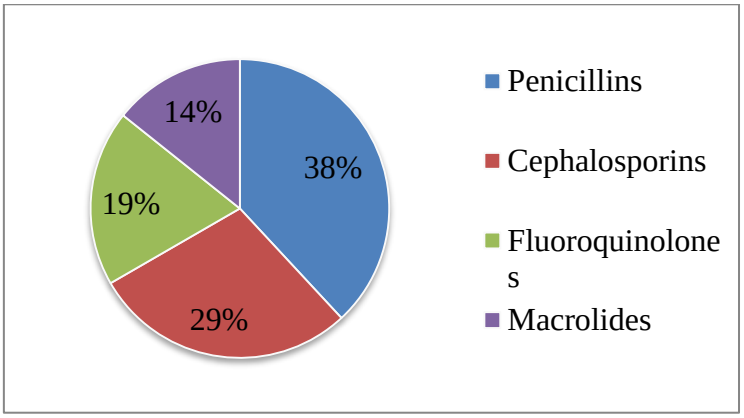
24% of patients (5 cases) who were treated with Amoxicillin/Clavulanic acid 1000 mg showed that the maximum level of AST is 50.2 U/L (0-31) and ALT 91.5 U/L (0-34). 10% of patients (2 cases) treated with Cefuroxime 500 mg and 14% (3 cases) with Ciprofloxacin 500 mg showed that the maximum level of AST in patients who were treated with Cefuroxime is 91.4 U/L (9-43) while ALT 100.4 U/L (10-41). In patients treated with Ciprofloxacin the maximum level of AST is 58.4 U/L and ALT 73.0 U/L. 9% of patients (2 cases) treated with Ceftriaxone 2 g IV showed a peak level of AST of 79.0 U/L and ALT of 123.0 U/L. 10% of patients (2 cases) treated with Clarithromycin 500 mg showed minimal increases in AST and ALT. The maximum level of AST is 48.7 U/L and ALT 50.2 U/L, which are shown in Graph 3.



Graph 3. The rate of increase in liver enzymes from the most prescribed antibiotics

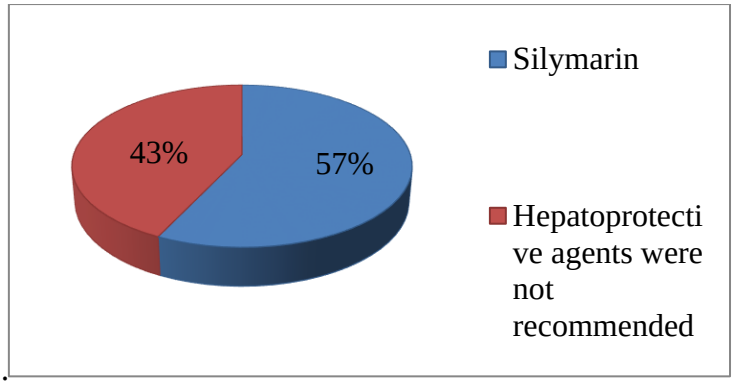
From the obtained results, it can be observed that slight, transient increases in aminotransferases appeared in patients treated with Fluoroquinolones and Macrolides, while patients treated with Penicillins, Cephalosporins developed increases in aminotransferases above twice the upper normal limit

The causative agents that developed liver enzyme values above the upper normal limit include Penicillins with 38% of patients (8 cases), followed by Cephalosporins 29% (6 cases), Fluoroquinolones 19% (4 cases), Macrolides 14% (3 cases), which are presented in Graph 4



*Graph **4. Groups of antibiotics that caused hepatotoxic** effects*

Among the hepatoprotective agents, mainly herbal preparations including Silymarin were recommended in 57% (12 cases), while in 43% (9 cases) no hepatoprotective agents were recommended, which are shown in Graph **5**



*Graph **5.** Use of hepatoprotective agents*

In this study, a wide variety of antibiotics resulted in hepatotoxic effects. Penicillins and Cephalosporins were the most common antibiotics that developed asymptomatic elevations of liver enzymes. Analysis of 29 cases showed that Amoxicillin/Clavulanic acid (Amoksiklav) was one of the most common antibiotics prescribed to outpatients that caused hepatotoxic effects after the end of treatment. Among the 6 patients who were treated with Amoxicillin/Clavulanic acid only 1 of them did not develop elevated liver enzymes. In cases of increased levels of liver enzymes that exceeded twice the upper limit of normal, doctors have recommended supportive therapy to patients - hepatoprotective agents to prevent progressive liver damage. Our results correspond to the data of (Raúl J. Andrade et al 2005) and others in the study conducted in Spain that was registered in the Spanish Registry of Hepatotoxicity where the analysis of 461 cases over a 10-year period showed that Amoxicillin/Clavulanic acid was the most common drug involved in hepatotoxicity

Conclusion

Antibiotics resulted in hepatotoxic effects. Penicillins and Cephalosporins were the most common antibiotics that developed asymptomatic elevations of liver enzymes
Elevated liver enzymes, fatigue, fever and jaundice are the most common symptoms.
Since Amoxicillin/Clavulanic acid is a widely used antibiotic, it is essential to highlight this side effect so that patients and medical professionals become more aware of its existence. By doing so, we hope to spare patients unnecessary examinations, which can be invasive and have potentially serious complications.
Some patients are asymptomatic and the identification of liver damage is based only on increased levels of liver enzymes; therefore, monitoring of liver tests is important to prevent serious effects. In addition, knowing the risk factors can prevent hepatotoxicity in a possible case because the process is reversible and the situation improves after withdrawal of the drug

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