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ANALYSIS OF AMOXICILLIN WITH THE COMPARISON OF CLAVULANATE IN LIVER INJURY

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Abstract:

Introduction: *The liver injury is reported often as secondary to hypersensitivity drug allergy resulting in centrizonal cholestasis, progressing to hepatocellular damage. In severe reactions, bile duct injury has been reported.* ***Objectives of the study:*** *The main objective of the study is to find the role of Amoxicillin with the comparison of Clavulanate for drug induced liver injury in hepatic patients.* ***Methodology of the study:*** *This case control study was conducted at Allama Iqbal Memorial Teaching Hospital, Sialkot during January 2019 to June 2019. For this purpose we select the 30 patients who was suffering from chronic hepatic injury due to the excessive use of drugs especially Amoxicillin and Clavulanate.* ***Results:*** *We analyzed 30 cases matched to controls. Seven cases were exposed to amoxicillin (adjusted OR 1.69, 95% CI 0.72-3.98) and 23 cases to co-amoxiclav (adjusted OR 3.00, 95% CI 1.76-5.40).* ***Conclusion:*** *It is concluded that compared to amoxicillin alone, amoxicillin +clavulanic acid doubles the risk of serious acute liver injury, in agreement with most studies on DILI.*

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INTRODUCTION:

The liver injury is reported often as secondary to hypersensitivity drug allergy resulting in centrizonal cholestasis, progressing to hepatocellular damage. In severe reactions, bile duct injury has been reported. The liver injury was mainly related to the clavulanic acid component; as a matter of fact, there are only few reports of hepatic reactions with amoxicillin alone. Drug-induced liver injury (DILI) is an important differential diagnosis in patients with abnormal liver tests and normal hepatobiliary imaging. Of all known liver diseases, the diagnosis of DILI is probably one of the most difficult one to be established. In all major studies on DILI, antibiotics are the most common type of drugs that have been reported[1]. The clinical phenotype of different types of antibiotics associated with liver injury is highly variable. Some widely used antibiotics such as amoxicillin vs clavulanate have been shown to have a delayed onset on liver injury and recently cefazolin has been found to lead to liver injury 1–3 weeks after exposure of a single infusion[2]. The other extreme is the nature of nitrofurantoin-induced liver injury, which can occur after a few years of treatment and lead to acute liver failure (ALF) or autoimmune-like reaction. Most patients with liver injury associated with use of antibiotics have a favorable prognosis[3]. However, patients with jaundice have approximately 10% risk of death from liver failure and/or require liver transplantation. In rare instances, the hepato toxicity can lead to chronic injury and vanishing bile duct syndrome. Given, sometimes very severe consequences of the adverse liver reactions, it cannot be over emphasized that the indication for the different antibiotics should be evidence-based and symptoms and signs of liver injury from the drugs should lead to prompt cessation of therapy[4].

Hepatotoxicity and drug-induced liver injury (DILI) are terms used interchangeably in this context. Drug-induced liver injury or DILI is the term currently used by most clinicians and scientists in this field. DILI can be defined as a liver injury induced by a drug or herbal medicines leading to liver test abnormalities or liver dysfunction with reasonable exclusion of other competing etiologies[5]. Most cases of DILI are due to idiosyncratic or unexpected reactions. In contrast to paracetamol-induced hepatotoxicity, which occurs with dose-dependent overdose of the drug, idiosyncratic drug reactions have been traditionally considered dose independent. However, drugs with well-documented idiosyncratic DILI have been shown to have a dose-dependent component[6].

For most drugs, hepatotoxicity is extremely rare and has been estimated to occur from 1 in 10 000 to 1 in 100 000 of those exposed to the drug, and for other drugs, the risk is probably even lower[7]. The number of included patients in most clinical drug trials is less than 10000 and hepatotoxicity has been mostly detected in the post marketing phase. The frequency of DILI among users of most drugs remains unknown and most epidemiological studies in this context suffer from major methodological limitations. There is uncertain accuracy in determining the relationship between the liver injury and the drugs reported in these studies. Most epidemiological studies are retrospective and lack standardized diagnostic work-up to exclude other potential causes of the liver injury. Moreover, most studies originate from tertiary referral centers and suffer from selection bias. Underreporting of adverse drug reactions is well known and DILI is no exception[8].

Objectives of the study

The main objective of the study is to find the role of Amoxicillin with the comparison of Clavulanate for drug induced liver injury in hepatic patients.

METHODLOGY OF THE STUDY:

This case ontrol study was conducted at Allama Iqbal Memrial Teaching Hospital, Sialkot during January 209 to June 2019.

For this pupose we select the 30 patients who was suffering from chronic hepatic injury due to the excessive use of drugs especially Amoxicillin and Clavulanate. Patients who suffer from DILI have a wide variety of clinical presentations. Clinically, biochemically and histologically, DILI can simulate almost all forms of acute and chronic liver injuries. Thus, these patients can present with acute liver failure with severe encephalopathy, with acute hepatitis with or without jaundice, and chronic hepatitis with both symptomatic and asymptomatic elevated liver tests.

Histopathology of liver

Tissues are fixed with neutral formalin 10%, embedded in paraffin, and then manually sectioned with a microtome to obtain 4-5 μm-thick paraffin sections. Dewaxed sections are then stained with hematoxylin and eosin (H&E) or can be used for other purposes (special stains, immunohistochemistry, in situ hybridization, etc.). During this process, many steps and procedures are critical to ensure standard and interpretable sections. Key recommendations are given here to achieve this objective.

Statistical analysis

Student's t-test was performed to evaluate the differences in roughness between group P and S. Two-way ANOVA was performed to study the contributions. A chi-square test was used to examine the difference in the distribution of the fracture modes (SPSS 19.0 for Windows, SPSS Inc., USA).

RESULTS:

Table 1 shows the baseline characteristics of these patients. Also these subgroups of patients did not reveal any significant differences between cases and controls, except for drug consumption.

Table 01: Analysis of characteristics of patients of both groups

	Amoxicillin		Clavulanate	
Characteristic	**Cases n=07**	**P value**	**Cases n=23**	**P value**
Sex, n (%)		0.09		0.14
Male	0 (0)		14 (59)	
Female	7 (100)		9 (41)	
Age (years), mean ± SD	42 ± 25.8	0.67	44.7 ± 17.8	0.65
BMI, mean ± SD	24.1 ± 6.8	0.77	24.6 ± 3.6	0.92
Alcohol, n (%)		0.99		0.51
Current drinker	4 (57)		16 (73)	
Former drinker	0 (0)		1 (4)	
Non-drinker	3 (43)		5 (23)	
Smoke, n (%)		0.17		0.99
Current smoker	3 (43)		7 (32)	
Former smoker	1 (34)		3 (14)	
Non-smoker	3 (43)		12 (54)	
Co-morbidities, n (%)				
Liver diseases	0 (0)	0.99	3 (14)	0.71
Heart diseases	2 (29)	0.99	2 (9)	0.99
Number of drugs, mean ± SD	6,9 ± 3,3	<0.001	4.9 ± 2.7	0.04

Table 2 shows the ANOVA results of both groups. It shows the degree of freedom and significant value of both groups with respect to control.

Table 02: ANOVA for drug induced hepatic injury

S.O.V	Sum of Squares	Df	Mean Squares	F	Sig.
Amoxicillin	12385.081	04	3096.270	23.794	.000
Clavulanate	2602.510	20	130.125		
Total	14987.591	24			

DISCUSSION:

The corresponding incidences are very low (0.1 cases for amoxicillin alone and 0.4 cases for amoxicillin +clavulanic acid for 100.000 inhabitant's year, respectively), in line with other estimates from published data[9].

The amoxicillin component of the drug is primarily excreted by renal system, whereas clavulanic acid is excreted by both the kidney and liver[10]. The mechanism of co-amoxiclav induced hepatitis is not completely clarified, but the frequent association with hypersensitivity reactions (i.e. skin rash, hypereosinophilia, anti-tissue antibodies) suggests an immune-allergic mechanism. The reaction could be due also to an idiosyncratic response to the drug[11]. Moreover, currently available evidence suggests a genetic susceptibility to coamoxiclav induced liver injury in patients with specific HLA haplotype. Although the absolute risk of co-amoxiclav-induced DILI is generally very low, as in the case of the present work, it must be also interpreted in relation to the widespread use of the drug, which continuously increased over the years[12].

CONCLUSION:

It is concluded that compared to amoxicillin alone, amoxicillin +clavulanic acid doubles the risk of

serious acute liver injury, in agreement with most studies on DILI.

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