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Original Research Article

To Study the Pattern of Drug Use and Safety of Medication Used in Liver Disease Patients at Tertiary Care Teaching Hospital

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Abstract:

Background: One of the most common non-communicable diseases, liver disease alters the pharmacokinetics of many medications, necessitating careful monitoring and dosing adjustments to ensure the best possible patient outcomes.

Aims and Objectives: The present study was undertaken to evaluate the drug usage pattern and its safety profile in liver disease patients.

Materials and Method: An observational and cross-sectional study was conducted in the department of medicine in a tertiary care teaching hospital from January 2020 to January 2021 after getting approval from the ethics committee. Male and female patients of all ages (below 12 years old) were included in the total of 100 people diagnosed with liver illness. Descriptive statistics were used to examine demographic information, clinical notes, medications prescribed, WHO prescribing core indicators, and adverse drug reactions.

Results: The majority of the study's participants (n=100) had non-alcoholic fatty liver disease. Liver disease was more common in men (74%) between the ages of 41 and 50. Antibiotics were prescribed to 77% of patients, and the average number of medications per patient was 8.17. Antibiotics made up 17.25% of all prescriptions written, while gastro protectives made up 23.9%. Cefotaxime was the most commonly given antibiotic (at 79%), with metronidazole coming in second at 32%. Antibiotics were responsible for the vast majority of reported adverse medication responses, including diarrhea, nausea, skin rashes, and AKT-induced hepatitis.

Conclusions: Disease-drug interactions are likely with the indiscriminate use of numerous medications because the liver is the primary organ for the metabolism of many pharmaceuticals.

Keywords: liver disease, drug use pattern, adverse drug reaction, NAFLD.

Introduction

The liver is the major organ involved in many physiological functions in our body. Any impairment in liver function can potentially alter the pharmacokinetics and pharmacodynamics of the drug. These changes generally can result in higher drug levels and possibly cause unwanted side effects and toxicity in patients.[1] Commonly prescribed drugs in hepatic disorders are antibiotics, proton pump

inhibitors, diuretics, laxatives, etc. Assessing the pattern of all drugs used in hepatic disorder is significant as most of the drugs get metabolized through the liver. Patients with liver disease require appropriate drug therapy for the etiology and also associated complications. Hence there is a need for this study to assess the prescribing pattern of drugs and to evaluate the adverse drug reactions observed, for better therapeutic outcomes.

Material and Methods

It was an observational and cross-sectional study conducted in the department of medicine in a tertiary care teaching hospital. The study was conducted for a period of one year from January 2020 to January 2021. All Liver disease patients (aged ≥ 12 years) old and newly diagnosed who were admitted to the medicine ward with elevated liver enzymes [aspartate aminotransferase (AST) & alanine aminotransferase (ALT)] than the normal range (normal range of AST and ALT is 10-40 IU/L, 7 to 56 IU/L) were included in the study. A total of 100 patients were analyzed during the study period.

The study was approved by the Institutional Ethics Committee. After taking informed consent to participate in the study patients' details were recorded from the case file including demographic details, co-morbid condition, clinical and treatment details, complications, and adverse drug reactions.

All data were collated using Microsoft Excel 2019 and descriptive statistics were used for detailed analysis. Demographic data that is continuous (age) is expressed as mean and standard deviation. Categorical data (Gender) is expressed as percentage.

Continuous variables are presented as mean ± standard deviation (SD). Adverse drug reactions were analyzed as percentages using descriptive statistics.

Results

Out of 100 patients, the majority of patients with liver disease were in the age group of 41-50 years followed by 51-60 years. The mean and standard deviation of the age of patients was 45.36 ± 1.27 years and it was observed that liver diseases were more in males (n=74) compared to females (n=26) (Table 1).

Table 1: Socio-demographic detail of patients (N=100)

Characteristics		Number of patients	Percentage
Gender	Male	74	74
	Female	26	26
Education	Literate	29	29
	Illiterate	71	71
Occupation	Employed	46	46
	Unemployed	54	54
Marital status	Married	67	67
	Unmarried	33	33
Area of domicile	Urban	58	58
	Rural	42	42

Associated co-morbid conditions were diabetes (n=21, 21%), diabetes + hypertension (n=5, 5%), hypertension (n=3, 3%), Hypertension + Ischemic Heart Disease (IHD) (n=3, 3%). Diabetes was the most common comorbid condition present in 21% of patients. In majority of the chief complaints observed were abdominal pain (n=73, 73%) and loss of appetite (n=72, 72%) followed by fatigue (n=67, 67%), abdominal distension (n=61, 61%), yellowish discoloration of sclera (n=56, 56%), nausea & vomiting (n=45, 45%) and edema (n=35, 35%).

In this study, 52 patients had non-alcoholic fatty liver disease and 17 patients had alcoholic liver cirrhosis followed by acute decompensated liver parenchymal disease (non-alcoholic type, n=10, 10%), viral hepatitis (n=7, 7%), obstructive jaundice (n=5, 5%), acute decompensated liver parenchymal disease (n=4,4%), liver abscess (n=2,2%), Anti Koch's treatment (AKT)induced hepatitis (n=2,2%)and Budd Chiari syndrome (n=1,1%).

Frequently associated complications in liver disease patients were jaundice (n=67, 67%) and portal hypertension (n=58, 58%) followed by ascites (n=50, 50%), anemia (n=23, 23%), variceal bleeding (n=15, 15%), hepatic encephalopathy (n=4, 4%) and hepatorenal syndrome (n=3, 3%). The major class of drugs prescribed were gastro protectives (n=196, 23.9%), antibiotics (n=142, 17.25%), diuretics (n=119, 14.56%), and vitamins (n=111, 13.58%).

Table 2: Drug utilization pattern among liver disease patients (N=100)

Class of drugs	Name of drugs	Number of drugs (%)
Gastroprotective	Ondansetron, Pantoprazole, Omeprazole, Ranitidine	196 (23.9)
Antibiotics	Cefotaxime, Metronidazole, Ceftriaxone, Cefoperazone + Salbactum, Clindamycin, Meropenem, Rifaximin, Amoxicillin + Clavulanic acid, Gentamycin, Piperacillin + Tazobactam, Ciprofloxacin, Amikacin	142 (17.25)
Diuretics	Furosemide	119 (14.56)
Vitamins	Calcium, Vitamin C, Folic Acid, Vitamin B Complex, Zinc, Injection Multivitamin	111 (13.58)
Parenteral Fluids	Normal saline, Ringer lactate, D25%, DNS	81 (9.91)
Antihypertensive	Propranolol, Metoprolol, Enalapril	65 (7.95)
Anti-Coagulants	Vitamin K	28 (3.42)
Laxatives	Lactulose	23 (2.81)
Protein Supplements	Albumin	16 (1.95)
Insulin		14 (1.71)
Others	Rifaximin (3), Thyroxin (2), Aspirin (1), Atorvastatin (1), Sodium Bicarbonate (2), Deriphylline (2),	11 (1.34)
Oral Hypoglycaemic Drugs	Metformin	4 (0.48)
Cholagogues	Ursodeoxycholic Acid	4 (0.48)
Antifibrinolytics	Tranexamic Acid	2 (0.24)
Coagulating Agent	Hemocoagulase (Botropase)	2 (0.24)
Total number of drugs prescribed		817

The major class of drugs prescribed were gastroprotectives (n=196,23.9%), antibiotics (n=142, 17.25%), diuretics (n=119, 14.56%) and vitamins (n=111,13.58%) (Table 2)

Among the antibiotics, metronidazole (n=79, 79%) was most commonly prescribed followed by cefotaxime (n=32, 32%) (Figure 1).

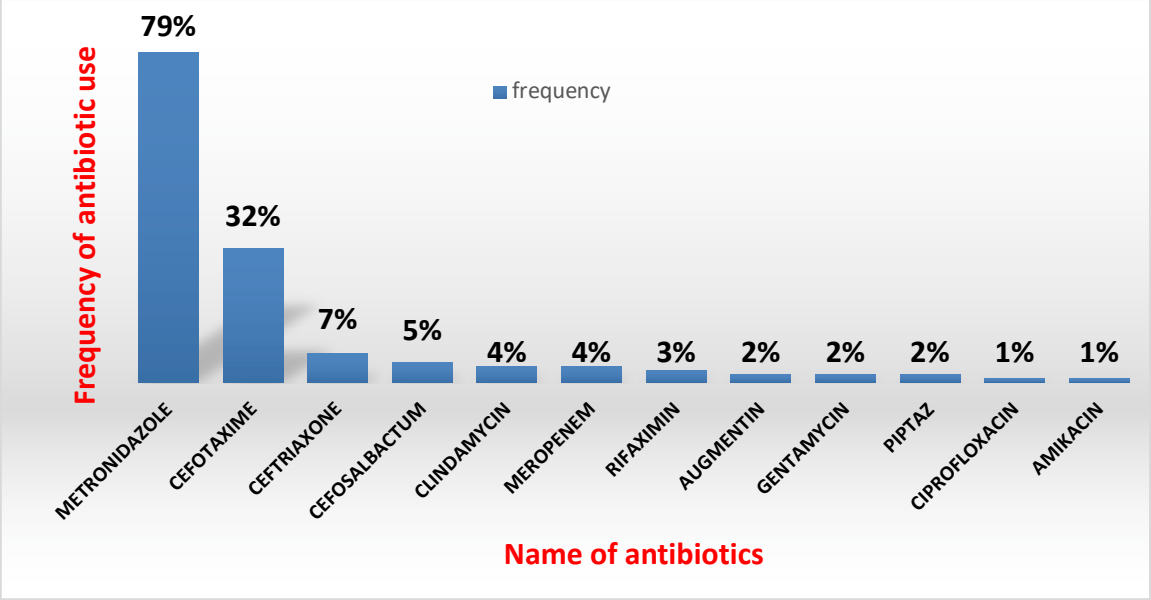

Figure 1: Distribution of antibiotics use (n=100)

WHO Prescribing Indicators, the average number of drugs per encounter among 100 patients was found to be 8.17 and the total number of patients who received antibiotics was 77% (Table3).

Table 3: WHO Prescribing indicators

WHO Prescribing indicators	Finding
The average number of drugs per prescription (n)	8.17
Percentage of drugs prescribed by generic name	78.94%
Percentage of drugs prescribed from WHO essential drug list (n)	79.06%
Total patients receiving antibiotics	77 (77%)
Total patients receiving injections	100 (100%)

Assessment of causality, severity, and preventability criteria was done by using World Health Organization (WHO) ADR probability scale, Hartwig& Siegel scale, and Modified Schumock& Thornton scale respectively. Most of the reactions were due to antibiotics. Two serious adverse drug reactions were Anti-Koch's Treatment (AKT) induced hepatitis which resulted in hospitalization. Other adverse drug reactions reported were pedal edema, skin rash, diarrhea, and nausea which were mild in nature and preventable. (Table 4)

Table 4: Analysis of adverse drug reaction (N=100)

Adverse drug Reaction	N	Suspected drug	WHO causality scale	Hartwig and Siegel severity scale level	Preventability Modified Schumock& Thornton scale
AKT induced hepatitis	2	AKT	Possible	Severe	Not Preventable
Pedal edema	2	Enalapril	Probable	Mild	Preventable
Skin rash	1	Amoxicillin + clavulanic acid	Probable	Mild	Preventable
Diarrhea	1	Piperacillin+ tazobactam	Probable	Mild	Preventable
Diarrhea	1	Clindamycin	Probable	Mild	Preventable
Nausea	1	Metronidazole, Cefotaxime	Possible	Mild	Preventable

Discussion

A variety of factors can damage the liver cells such as viral infections, genetic conditions, autoimmune disorders, cancer, and certain drugs. Several potential risk factors can also be associated with liver disease such as excessive consumption of alcohol, type 2 diabetes, obesity, high cholesterol, and injecting drugs using shared needles.[2] Further complications in liver disease lead to acute kidney injury (AKI) and hepatorenal syndrome due to fluid retention in case of ascites, edema or portal hypertension.[3] Alcoholic liver disease and non-alcoholic fatty liver disease are both serious health and socioeconomic problems increasing worldwide. No single therapy for any liver disease has been proven to be effective. Various treatment modalities used for the prevention and treatment of liver disease have included lifestyle modifications such as weight loss and exercise and treatment of risk factors.

A hurdle for prescribers arises from the fact that hepatic impairment frequently modifies the pharmacokinetic and/or pharmacodynamic effects of medication. In the present study, the mean age of the patients was around 45 years with more patients from the age group of 41-50 years as compared to the age group of 51- 60 years which was comparable with the study done by Vuddanti S et al.[4] and Zeebaish S et al [5].

It shows that liver diseases are more prevalent in the elder age group. Furthermore, the aging-associated decline in mitochondrial function has been shown to enhance the vulnerability to injury. Insulin resistance, which is known to be a primary cause of NAFLD, is a major component of metabolic syndrome, which is often observed in elderly people. [6]

The physiological differences between males and females lead to a few liver-related gender disparities. In the present study, the majority of the patients were male (74 %) which was similar to the study done by Vuddanti S et al [4], Menu V et al [7], and Huma S et al [8] where the majority of them were male patients indicating that there is a higher prevalence of liver disease in male than female patients. In the present study, the proportion of illiterate patients (n=71) is more compared to literate patients (n=29). Diabetes mellitus, tobacco chewing, central obesity, low education, and the low-income group were all found to be significant risk factors for chronic liver disease in the population in a case-control study conducted by Banait S et al [9] in central India.

In the present study, among 100 patients 58 (58%) patients reside in urban areas while the other 42 (42%) patients are from rural areas. This is similar to the study done by Menu V et al [7] where 57.33% of the patients were from urban areas and the remaining (42.67%) were from rural areas. Desai N et al [10] also observed similar results. Diabetes and cardiovascular (CVS) disorders are common comorbidities associated with liver disease. In our study, diabetes (n=21) is the most commonly associated co-morbid condition followed by diabetes with hypertension (n=5), hypertension (n=3), and hypertension + infective heart disease (n=3). The study done by Vuddanti et al [4] (N=100) found the comorbidities like diabetes (n=11), hypertension (n=11), and diabetes plus hypertension (n=8). Diabetes and hypertension were commonly observed as co-morbid disorders in studies conducted by Zeebaish S et al.[5], Huma S et al.[8], Sugali et al.[11], and Desai N et al.[10]. It is common practice to overmedicate the elderly with medications that interact with one another and increase the risk of hepatotoxicity.[12]

Symptoms of liver disease can remain clinically unapparent for long periods and can become evident only after liver failure sets in or a large proportion of the liver is compromised functionally. In this study, patients are presented with chief complaints like abdominal pain (n=73), loss of appetite

(n=72), fatigue (n=67), abdominal distension (n= 61), yellowish discoloration of the sclera (n= 56), nausea & vomiting (n=45) and edema (n=35). Sugali V et al [11] found pedal edema (n=91) and abdominal distension (n=86) out of 160 patients followed by icterus, abdominal pain, vomiting, and loss of appetite.

Chronic liver disease as a result of non-alcoholic fatty liver disease and alcoholic liver disease is a significant public health concern. Currently, the prevalence rate of liver disease is increasing in our country and to know their prevalence in our setup, a disease-wise classification of patients was carried out.

The patients were classified into various diseases like non-alcoholic fatty liver disease (n=52), alcoholic liver disease (n=17), liver parenchymal disease (non-alcoholic type n=10, alcoholic type=4), viral hepatitis (n=7), obstructive jaundice (n=5), liver abscess (n=2), Budd Chiari syndrome (n=1) and AKT induced hepatitis (n=2). We observed that the prevalence of non-alcoholic fatty liver disease (n=52) is more compared to other types of liver disease and very few patients comprise alcoholic liver disease (n=17). Desai N et al. [9] (N=137) found a similar pattern, concluding that non-alcoholic liver disease (NAFLD) was responsible for 75% of the liver damage compared to alcoholic liver disease's 25% contribution. While Belbase N et al [13] found a higher frequency of alcoholic liver disease (n=63) in Karnataka, this could be attributable to differences in geographical location, dietary habits, and socioeconomic status. Strong clinical risk factors for fibrotic progression of non-alcoholic fatty liver disease include changes in lifestyle, obesity, type 2 diabetes mellitus, poor eating habits, pollution, and smoking, all of which contribute to the illness's widespread occurrence. The prevalence of NAFLD is rising as these risk factors become more common.

In the present study, many complications are associated with liver disease. Jaundice (n=67) and portal hypertension (n=58) were the major complications associated with liver disease followed by ascites, anemia, variceal bleeding and the least observed but serious complications like hepatic encephalopathy and hepatorenal syndrome. Patients have portal hypertension, jaundice, anemia, and hepatorenal syndrome, as was also shown in a study by Zeebaish S et al[5]. In contrast, portal hypertension and ascites, followed by anemia and jaundice, were the most common consequences in the study by Biradar SM et al [14] (N=130).

Among the total 817 medications prescribed to 100 patients in the current study, gastro protectives (n=196) were the most common, followed by antibiotics (n=142), diuretics, vitamins, parenteral fluids, antihypertensive, anticoagulants, laxatives, protein supplements, insulin, cholagogues, oral hypoglycemic drugs, antifibrinolytics, coagulating agents, and others.

A similar drug prescription pattern was found in Vuddanti et al, [4]Huma S et al [8] and Biradar SM et al [14], where the total number of medications prescribed was 1024, 1135, and 687 respectively, in which gastro protectives, antibiotics, diuretics and vitamins are the most commonly prescribed category of drugs in liver disease patients. A study done by Meenu V et al [7] and Sugali V et al [11] reported that antibiotics and vitamins were most commonly prescribed followed by antacids and diuretics.

Gastro protectives prescribed in our study were omeprazole, ranitidine, pantoprazole, and laxatives like lactulose. The reason for prescribing gastro protectives in most patients is because of gut dysfunction associated with cirrhosis which impacts the quality of life and nutritional status as well as the development of cirrhosis complications. [15]

The increase in antibiotic-resistant bacteria poses a major healthcare threat.[16] In the present study, antibiotics were the 2nd most commonly prescribed category. A total of 142 antibiotics were prescribed and the most commonly prescribed antibiotic was metronidazole (n=79) followed by cefotaxime (n=32), ceftriaxone (n=7), and cefoperazone + sulbactum (n=5). Others were clindamycin, meropenem, rifaximin, amoxicillin + clavulanic acid, gentamycin, piperacillin + tazobactam, ciprofloxacin, and amikacin. Another study done by Vuddanti S et al [4] found that a total of 154 antibiotics were prescribed and cefotaxime (n=53) was used predominantly followed by cefoperazone and metronidazole. In the study done by Sugali V et al, [11] total number of prescribed antibiotics was 249, and cefotaxime (n=95) was the foremost prescribed antibiotic followed by rifaximin, metronidazole, and ceftriaxone. A study done by Zeebaish S et al [5], Meenu V et al [7], and Huma S et al [8] noted that 3rd generation cephalosporin was the most commonly prescribed class of antibiotics in patients with liver disease.

Diuretics like spironolactone and frusemide were the next commonly prescribed to prevent the recurrent occurrence of ascites. Vitamin supplements were prescribed to combat vitamin deficiency associated with the development of liver disease. According to WHO Prescribing Indicators, the average number of drugs per prescription among 100 patients was 8.17 whereas in the study done by Vuddanti S et al, [4]Sugali V et al [11] and Zeebaish S et al [5] average number of drugs per prescription are 7.5, 9.13 and 9 respectively. The number of drugs prescribed was higher in liver disease patients because of the complications and associated comorbid conditions. In the current study, the percentage of drugs prescribed by generic name was found to be 78.94% which is similar to the study done by Sugali V et al (78.97%). [11] Whereas, in the study done by Vuddanti S et al [4], and Zeebaish S et al [5] generic names were prescribed in 60.17% and 45.76% respectively. Moreover, according to the result of this study, 79.06% of drugs were prescribed from WHO essential drug list. Likewise, Zeebaish S et al [5] found 82.11 % and Sugali V et al [11] found only 61.51% of drugs prescribed from the WHO essential drug list. Regarding antibiotics, in the current study, the percentage of encounters where antibiotics were prescribed was 77% which is similar to the study done by Zeebaish S et al. [5] in which they found 74.34% of patients receiving antibiotics whereas in the study done by Vuddanti et al [4] and Sugali V et al [11] all the patient received antibiotics. In our settings, the percentage of patients prescribed injectables was 100% which is similar to the study done by Zeebaish S et al [5] and Sugali V et al [11].

In the present study, an analysis of adverse drug reactions was also carried out among 100 patients. We found 8 adverse drug reactions and most of them were due to the antibiotics. More commonly reported adverse drug reactions were diarrhea (n=2), nausea (n=1), skin rashes (n=1), and AKT (Anti-Koch's Treatment) induced hepatitis (n=2). Diarrhea was reported due to the suspected drug piperacillin + tazobactam and clindamycin, nausea was reported due to metronidazole and cefotaxime and skin rash was caused by amoxicillin + clavulanic acid. Hepatitis was due to the 1st line of anti-tuberculosis drugs. Two cases of Enalapril-induced pedal edema were also reported. While in the study done by Naranjo C.A. et al [17] (N=1280) most commonly associated adverse drug reaction was with diuretics (32.6% of patients receiving the drugs), parenteral solutions (10.8%), potassium salts (6.5%), antimicrobials (3.9%) and sedatives (3.5%).

Drugs like methotrexate, cytotoxic drugs, aspirin, and sodium valproate may enhance the chance of developing drug-induced hepatic damage in those with pre-existing liver disease. ADRs are more common in

people who already have liver dysfunction. One of the most difficult types of acute or chronic liver disorders for doctors to treat is drug-induced liver injury (DILI). Drug-induced liver injury (DILI) is a common cause of acute liver failure despite its low prevalence in the general population. For antibiotics specifically used for tuberculosis, adverse effects range from an asymptomatic increase in liver enzymes to acute hepatitis and fulminant hepatic failure. [18] In the present study, 2 cases of AKT-induced hepatitis were noted which were possibly related to the adverse reaction and severe and also not preventable. The incidence of first-line anti-TB drug-induced hepatotoxicity was found to be 8.9% in Ethiopia (N=216). [19] Here, in our study another adverse drug reaction of pedal edema induced by enalapril in 2 cases was also noted which is probably related to the adverse drug reaction, mild in nature and preventable. Because ACE inhibitors like enalapril require conversion to enalaprilat which is reduced in patients with well-compensated liver cirrhosis and impaired liver function compared to healthy individuals.

Causality assessment for each adverse drug reaction was done in this study by using WHO-UMC causality assessment scales. [20] Maximum cases were classified as 'probable'. No 'certain' ADR on the WHO-UMC scale was found since the re-challenge was not performed by the clinician once the drug was withdrawn. Most of the reactions reported were of mild severity which included diarrhea, nausea, skin rash, and pedal edema. There were 2 cases of severe-level adverse drug reactions reported which included drug-induced hepatitis due to Anti-Koch's Treatment (AKT). In the preventability assessment, all ADRs were found to be preventable except drug-induced hepatitis due to Anti-Koch's Treatment (AKT) which was not preventable.

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