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Original Research Article

Evaluation of prescribing pattern of drugs and compliance to standard treatment guidelines in patients of chronic hepatitis B: a prospective observational study

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ABSTRACT

Background: Hepatitis B is a major global health problem. Chronic hepatitis B is characterized by hepatic inflammation, necrosis and persistence of HbsAg for at least 6 months. Chronic liver disease is more predictably associated with impaired metabolism of drugs than acute liver dysfunction. Prescribing drugs in patients with chronic hepatitis B is challenging because of concerns that the drug may exacerbate the liver disease. There is also the fear that the altered liver state may change metabolism and excretion of the drug.
Methods: A cross-sectional prospective study was conducted involving patients diagnosed with chronic hepatitis B at the liver clinic outpatient department (OPD) of AIIMS Bhopal. A total of 102 patients with chronic hepatitis B who met the inclusion criteria were recruited in the study.
Results: Out of 102 prescriptions, 492 drugs were prescribed for the 102 patients. Out of 102 patients, 81 patients (81.66%) were on entecavir monotherapy and rest 21 patients (18.34%) were on tenofovir disoproxil fumarate (TDF) monotherapy. Of the 102-prescription issued, 92.15% (94/102) were compliant and 7.85% (8/102) were noncompliant.
Conclusions: Entecavir was the most common antiviral drug prescribed, followed by tenofovir in patients of chronic hepatitis B. Spironolactone plus torasemide combination was the most common fixed dose combination used among study participants. Liver cirrhosis followed by portal hypertension was the most common complication. Majority of prescriptions were compliant with recommendations for pharmacotherapy and safety guidelines in patients of chronic hepatitis B.

Keywords Chronic hepatitis B, Prescribing pattern, Antiviral drugs, Compliance to guidelines

INTRODUCTION

Chronic hepatitis B is a global health problem. Chronic hepatitis B is characterized by hepatic inflammation, necrosis and persistence of HbsAg for at least 6 months.[1] As was reported in the global hepatitis report of the WHO, it was estimated that 257 million people were living with chronic hepatitis B virus (HBV) in 2015.[2] The long-term complications include liver cirrhosis and hepatocellular carcinoma (HCC), which were estimated to cause about 887,000 annual deaths.[2] Serious complications of chronic hepatitis B (CHB) include cirrhosis, liver failure and hepatocellular carcinoma which accounts for a global death rate of 1 million cases annually.[2-4] Advanced phases of liver disease, older age, male gender, Hepatitis B virus (HBV) genotype C and high HBV DNA viral load increase the risk for HCC devolvement.[5]

There are several approved treatments for CHB including interferon-alpha, pegylated interferon-alfa (PegINFa) and six different nucleotide analogue (NUCs). These include entecavir, tenofovirdisoproxil fumarate and TDF, lamivudine, telbivudine, adefovir. The first line oral drugs are tenofovir and entecavir. The second line oral drugs are lamivudine, adefovir & telbivudine Since the liver is the primary site of drug metabolism, knowledge of a patient's liver function is required for the safe prescribing of many drugs. Since liver is the major site for drug metabolism and biotransformation, chronic liver disease is more likely to affect drug metabolism. The changes in drug metabolism due to chronic liver disease are complex and there is no simple test like creatinine clearance for renal disease so, drugs should be prescribed carefully in patients of chronic liver disease. Till now, very few studies have been conducted for evaluation of drug prescribing in patients of chronic hepatitis B. So, we have planned this study to evaluate prescribing practices in patients of chronic hepatitis B. American Association for the study of liver disease (AASLD)provides evidence-based guidelines on the treatment of chronic hepatitis B (CHB) virus (HBV) infection in adults and children.[6] The goals of antiviral treatment are to decrease the morbidity and mortality related to CHB. There is also the fear that the altered liver state may change metabolism and excretion of the drug.[7] About 50% of drugs have been associated with liver injury, and more than 100 drugs are implicated in fulminant hepatic failure, and 10% of all adverse drug reactions are hepatotoxic effects.[8]

Patients with chronic hepatitis B require appropriate drug therapy for the etiology and also the associated complications. Drug formulary references give recommendations on drugs that should be used with caution and when unavoidable, their dosage be adjusted in patients with chronic hepatitis B.[9] The WHO, European association for the study of liver disease (EASL), and American association for study of liver disease (AASLD) among others provide recommendations for the prescribing of drugs in the chronic liver disease.[10] A review of literature, however, indicates that there are few drug utilization studies among chronic hepatitis B patients in central India. The aim of this study was to assess the prescribing pattern of drugs in patients of chronic hepatitis B along with compliance of pharmacotherapy as per evidence-based guidelines and drug formulary recommendations.

METHODS

Study design and site

A cross-sectional prospective study was conducted involving patients diagnosed with chronic hepatitis B at the liver clinic outpatient department (OPD) of AIIMS Bhopal. AIIMS Bhopal is a tertiary care hospital for the central India. Approval was taken from institutional human ethics committee (IHEC) to conduct this study. (LOP no. IHEC/AIIMS/BPL/IM043). Written informed consent was obtained from all the participants enrolled in the study.

Patients and inclusion criteria

Patients visited at the liver clinic of AIIMS Bhopal hospital between October 2022 to May 2023, and diagnosed with a chronic hepatitis B were eligible for the study. Patients were only included in the study if they were >18 years of age, willing to provide written informed consent and documented diagnosis of chronic hepatitis B characterized by significantly raised SGPT (> 2 times of upper limit normal), detection of HBsAg, IgG anti-HBc, HBeAg and significantly raised HBV DNA (HBV DNA is >20000 IU/ml) in PCR based assay. The exclusion criteria were patients co-infected with hepatitis C, hepatitis D or human immunodeficiency virus, acute or decompensated hepatitis B, hepatitis B carrier statediagnosed by absence of HBeAg and presence of anti-HBe, undetectable or low levels of HBV DNA in PCR-based assays, repeatedly normal SGPT levels, pregnant and lactating women and diagnosed psychiatric illness.

Data collection

Data was collected from the patient's outpatient records, using a case record form. Patient's demographic data included age, gender, socioeconomic status, family history and occupation. Clinical data collected were clinical presentations, disease severity and stage, comorbid illness, history of alcohol intake, treatment history, investigation reports and other complications of chronic hepatitis B. Diagnosis of the complications of chronic hepatitis B was made according to the AASLD criteria. Severity of the chronic hepatitis B was assessed according to the child Pugh's classification. Data on drug treatment consisted of all medications prescribed and complications of chronic hepatitis B.

Assessment of compliance with guidelines

Compliance with pharmacotherapy was assessed in two categories: according to recommendation for prescribing first choice therapy and recommendation for safe prescribing. In assessing compliance, according to first choice therapy, American association for study of liver disease (AASLD), was used. With respect to safe prescribing, the safety recommendations by Weersink et al and dosing considerations in liver impairment by the British national formulary was used.[11] Descriptive statistics of the patients' demographic and clinical characteristics were performed and summarized in percentages and presented in tables. Statistical package for social sciences (SPSS), version 27 was used for the data analysis.

RESULTS

A total of 102 patients with chronic hepatitis B who met the inclusion criteria were involved in the study, with

majority (71.7%) being males. The mean (SD) age of the patients was 49 years, and most (43.4%) of them were in the 40-70-year group (Figure 1). With respect to severity of the disease, almost half (49%; 74/152) of the patients were of class B (moderate chronic hepatitis B), with a little above 10% (16/152) being in class A (mild chronic hepatitis B) and rest in class C (40.33%) (Figure 2).

There were 102 prescriptions episodes comprising 492 drugs written for the 102 patients studied. Out of 102 patients, 81 patients (81.66%) were on entecavir monotherapy and rest 21 patients (18.34%) were on TDF monotherapy (Figure 3). The top 10 therapeutic classes of medicines utilized for the management of complications of chronic hepatitis B are presented in Figure 4. Liver cirrhosis was the most common complication followed by portal hypertension, hypoalbuminemia, ascites, gastroesophageal varices, jaundice and spontaneous bacterial peritonitis (SBP) (Figure 5).

A total of 492 drugs were prescribed, with antivirals were the most utilized class 83.07% (408/492) followed by propanolol. Propranolol with 62.98% (305/492) was the only agent prescribed under the class of beta-blockers. Antibacterial agents were the next most utilized class at 19.25% (93/492) and blood products being the least at 3.78% (19/492). Among the antibacterial agents, metronidazole was the most prescribed with 25.22% prescriptions written. Spironolacone made up the majority of the diuretic prescriptions, with 58.56% (285/492) made to 55 patients. A combination of spironolactone and torasemide was the most common fixed drug combination prescribed in 42% of patients. Paracetamol with 58.11% (285/492) was the major analgesic prescribed to 49% of patients. Among the vitamin supplements, vitamin B complex at 35.22% (172/492) was the most, with 69 prescriptions. The main prescribed drug among the anti-acid-secreting agents was pantoprazole with 82 prescriptions. Among the 90 hematinics, folic acid, 34 (37.87%), and ferrous sulphate, 33 (36.71%), constituted the main prescribed agents. Prescription pattern of blood products indicated albumin to be the highest prescribed (182/492).

Compliance with guideline recommendations

Out of 102 prescriptions issued, 92.15% (94/102) were compliant and 7.85% (8/102) were noncompliant to standard treatment guidelines. With regard to first choice therapy, six prescriptions written were noncompliant. Metronidazole was the highest in this category, with four prescriptions. (Table 1). According to safe prescribing guideline recommendations, eight prescriptions were not compliant (Table 2). A total of four prescriptions of metronidazole higher than the maximum dose were made to patients. Paracetamol was prescribed in more than recommended doses in two prescriptions. A total of two prescriptions of tramadol paracetamol fixed dose combinations were prescribed which was more than recommended doses.

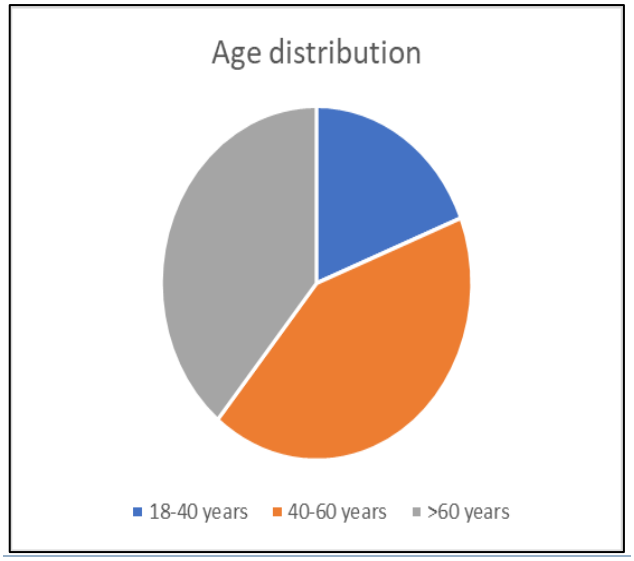

Figure 1: Age distribution in patients of chronic hepatitis B.

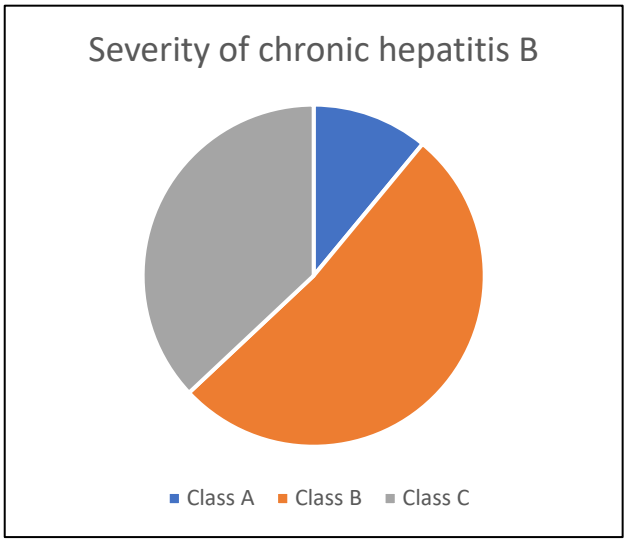

Figure 2: Severity of chronic hepatitis B as per CPT class A, B and C (Child Pugh).

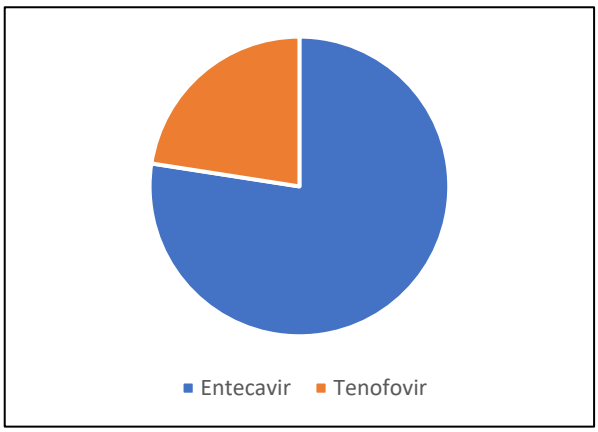

Figure 3: Antiviral drugs prescribed in patients of chronic hepatitis B.

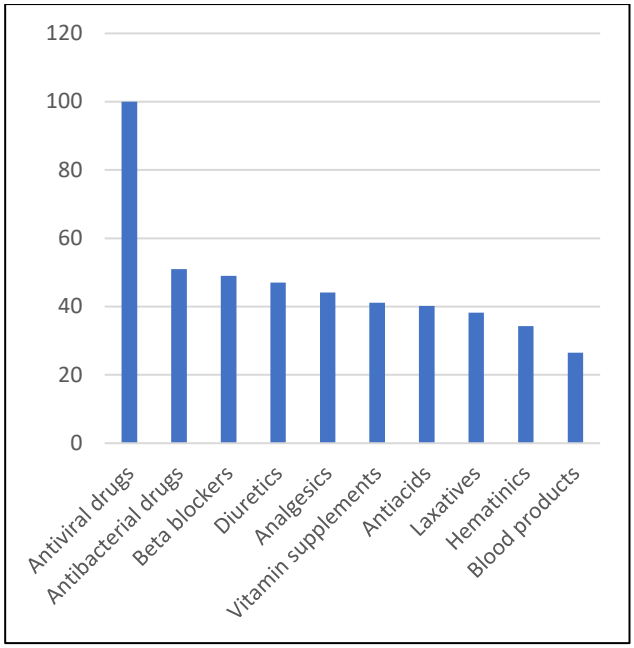

Figure 4: Different drug classes prescribed in patients of chronic hepatitis B.

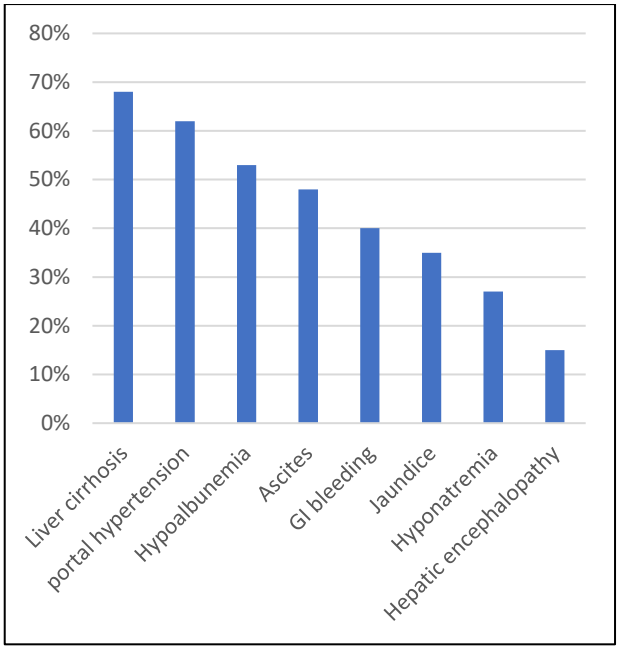

Figure 5: Distribution of various complications in chronic hepatitis B.

Table 1: Prescriptions not compliant with pharmacotherapy guidelines for indication (n=06).

Drug	Indication	Comment	No. of prescriptions
Metronidazole	Spontaneous bacterial peritonitis (SBP)	Not first choice	04
Tramadol paracetamol fixed dose combination	As an analgesic	Not first choice	02

N: total number of prescriptions not compliant according to indication; CHB: chronic hepatitis B, SBP: spontaneous bacterial peritonitis, FDC: fixed dose combination.

Table 2: Prescriptions not compliant with safety prescribing guidelines (n=8).

Drug	Comment	Number of prescriptions
Paracetamol	Maximum dose exceeded	02
Paracetamol plus tramadol (FDC)	Incorrect dose and frequency	02
Metronidazole	Incorrect dose and frequency	04

DISCUSSION

Similar studies were conducted by Mohammed et al for evaluation of drug prescribing in patients of liver cirrhosis due to chronic liver disease in Ghana.[12] They reported that substantial number of prescriptions were not as per recommended guidelines. In contrast to their study, our study concludes that majority of prescriptions were as per recommended guideline which was a favourable finding of our study. However, they conducted their study in indoor patients and also included the patients of chronic liver disease due to CHB, chronic hepatitis C, hepatocellular carcinoma, alcoholic hepatitis and cryptogenic hepatitis. In contrast to their study, in our study recruited only outdoor patients of chronic hepatitis B.

Jeong Lee et al reported that with the development of new drugs and the changes in clinical practice guidelines, the prescription pattern of the antiviral agents for patients with CHB has changed.[13] The rate of utilization of tenofovir has increased. But in our study, entecavir was the most common drug that was used for the treatment of chronic hepatitis B. Entecavir was used in majority of patients because entecavir has been recommended as first line drug in patients of advanced disease. In our study, most of the patients were in advanced stage of chronic hepatitis B. This was the reason for more prescription of entecavir. Entecavir is highly potent; it confers a good barrier to the development of resistance from the HBV.

Analysis of drug prescribing compliance with recommendations of pharmacotherapy guidelines revealed that majority of prescriptions were as per standard treatment guidelines. All patients were prescribed first line

antiviral drugs as per recommended guidelines i.e., entecavir or tenofovir. None of the second line drugs were prescribed in our study. Both lactulose and rifaximin are recommended in patients of chronic hepatitis B, who are at risk of development of hepatic encephalopathy. Rifaximin is used for gut sterilization. Majority of patients were prescribed both lactulose and rifaximin, which was as per standard treatment guideline.

Evaluation of treatment of complications revealed minor deviation with guideline recommendations. Metronidazole was prescribed for prophylaxis and treatment of spontaneous bacterial peritonitis (SBP) in four prescriptions. Metronidazole has typical anaerobic spectrum and a relatively little effect against aerobic bacteria and as such is not recommended for SBP. Anaerobic organisms are rare in SBP because of the high oxygen tension of ascitic fluid.[14] Typically, SBP is caused by aerobic organisms, about 75% by aerobic gram-negative organisms and the remaining 25% due to aerobic gram-positive organisms.[15] Third-generation cephalosporins and fluoroquinolones, are recommended for empirical treatment and prophylaxis of SBP.[16,17] In the current study, there was noncompliance with guidelines on safety and dosing recommendations. Metronidazole is recommended to be prescribed at a dose of one-third of the total daily dose 24 hourly or at 50% dose reduction in patients with severe hepatic impairment (Child Pugh C).[18] This downward adjustment of dose is essential to match the reduced metabolism of metronidazole, which has been shown to increase its elimination half-life with manifestation of adverse effects in severe hepatic impairment.[19] In more than 20% of the patients with severe hepatic impairment (Child Pugh C) studied, the prescriptions of metronidazole were not compliant with guideline recommendation of dose reduction.

In our study, paracetamol was the most common analgesic that had been prescribed in patients of chronic hepatitis B, which was prescribed in more than recommended dose (2.0 grams) in two prescriptions. drug induced liver injury (DILI) accounts for more than 50% of the cases of acute liver failure, with paracetamol being the principal offending agent.[20] Drug induced hepatotoxicity is the most common reason for the culprit drug to be withdrawn from the market, with more than 900 drugs being implicated in causing the same. Five percentages of all hospital admissions and 50% of all acute liver failures are found to be drug induced, which can even result in liver transplantation or death.[21] Although paracetamol can produce hepatotoxicity at higher dose, still it can be safely prescribed at lower dose i.e., up to 2 gm per day as per standard treatment guidelines. A 3 times elevation of the upper limit value of ALT levels is considered as a biochemical marker for liver injury. According to Hyman Zimmerman, elevated ALT accompanied by jaundice was associated with 5-50% mortality and this observation has since been referred to as "Hy's rule". This rule is currently used by the FDA in the evaluation of hepatotoxicity for newly developed drugs, before approval.[22]

Proton pump inhibitors (PPIs) are one of the most commonly used and misused drugs. They should be used judiciously in patients of hepatic impairment, since excessive use of PPI is associated with various adverse events like infections and development of hepatic encephalopathy.[23] Majority of the patients were prescribed pantoprazole which was as per standard treatment guidelines. Spironolactone plus torsemide was the most commonly prescribed FDC in our study. Spironolactone is an aldosterone receptor antagonist and potassium sparing diuretic. It is commonly used in the hepatic edema, especially in patients with cirrhosis in which hyperaldosteronism play a major role. Torasemide is a high ceiling loop diuretic. Spironolactone antagonize potassium loss induced by high ceiling diuretics. It breaks resistance to diuretics that develops due to secondary hyperaldosteronism.

Use of opioid paracetamol combination is harmful, because addiction to the opioid may occur with a gradual increase in opioid paracetamol combination dosing over days or weeks. Within opioid combination products, the limit for the paracetamol component has been lowered to 325 mg per tablet. Analysis of tramadol prescription revealed that 17% of patients with child Pugh C had their dose frequency higher than recommended. Tramadol is recommended in a dose of 50 mg 12 hourly in severe hepatic impairment as per standard treatment guidelines. Opioids are generally recommended to be used cautiously and initiated with intermediate-release formulations at low doses with extended frequency of administration in patients with liver impairment because of potential accumulation.[24] Majority of prescriptions were compliant with recommendations for pharmacotherapy and safety guidelines in patients of chronic hepatitis B which was a favourable finding of this study. Weersink and co-workers provide a useful resource that can guide all health personnel to attain optimal pharmacotherapeutic management of patients with liver diseases.[11]

Limitations

Our study was conducted in only outdoor patients of a single hospital. Large multicentric studies in both indoor and outdoor patients is required to extrapolate the results for larger population.

CONCLUSION

Entecavir was the most common antiviral drug prescribed, followed by TDF in patients of chronic hepatitis B. Spironolactone plus torasemide was the most common fixed dose combination prescribed in patients of chronic hepatitis B for the treatment of ascites. Liver cirrhosis followed by portal hypertension was the most common complication in study participants. Majority of prescriptions were compliant with recommendations for pharmacotherapy and safety guidelines in patients of chronic hepatitis B. Healthcare professionals should be

sensitized about rational use of drugs in patients of chronic liver disease as per evidence-based guidelines.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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