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Evaluation of Use of Hepatitis B Drugs in Hospitalized Patients at "X" Hospital Semarang in the Period from January 2015 to December 2016

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Abstract

Background: Hepatitis B is a liver disease caused by the hepatitis B virus which can cause acute or chronic liver inflammation that can lead to liver cirrhosis or liver cancer. Patients with hepatitis B virus infection can be given hepatoprotector drugs, cholelitolytic drugs and antiviral drugs. The purpose of this study was to determine the characteristics of hepatitis B patients and evaluation of the use of each hepatitis B drug in hepatitis B patients. The evaluation includes appropriate indication, appropriate medicine, appropriate patient, appropriate dosage, and evaluation of potential drug interactions during therapy.

Methods: This study was an observational study, with a cross-sectional design. Data retrieval is done by purposive sampling. Inclusion criteria are patients with acute hepatitis or chronic age 26-45 years who have been approved laboratory tests, with or without complications. The type of qualitative data includes the type of drug and the dose given, then compared with the literature to assess accuracy. Results of the assessment of conformity with the literature and accuracy verified in percent.

Results: The results obtained 61 patients who met the inclusion criteria with characteristics based on sex were found to be the most common in males (73.77%) and age range 41-45 years (37.70%) at the most. Evaluation of the use of each hepatitis B drug in this study obtained results: appropriate indication for hepatoprotector drugs (100%) and antiviral drugs (81.97%), appropriate medicine (100%), appropriate patient (100%), and appropriate dosage (100%). There is 1 type of potential drug interaction in the treatment of hepatitis B with other drugs, namely between alpha 2-a interferon and ondansetron as many as 3 cases (4.92%).

Keywords: Hepatitis, Hepatitis Drugs, Accuracy, Potential Interactions

INTRODUCTION

Hepatitis B is a liver disease caused by hepatitis B virus. (1) Transmission of hepatitis B occurs through contact with the patient's body fluids. If the disease is not handled properly, it can cause chronic liver disease and even cirrhosis of the liver and liver cancer which is at high risk of causing death. (2)

Patients with acute hepatitis B only need supportive care. (3). Antiviral therapy is indicated for hepatitis B fulminant, severe hepatitis, jaundice with bilirubin> 10 mg / dL, infection along with the presence of hepatitis C or D. virus (4). The use of interferon can increase the risk of hepatic necro-inflammation, so it needs to be avoided. An acceptable choice for chronic hepatitis B is tenofir, telbivudine, and entecavir nucleoside analogues given monotherapy in short-term use (4,5) and lamivudine, adefovir, dipivoxil. (5) In April 2018, CNN Indonesia reported that a study published in the journal Lancet Gastroenterology and Hepatology, only 1 in 20 people contracted HBV who received appropriate medical treatment. Data on the price of antiviral drugs for hepatitis B can reach 500 thousand - 1 million per month.

Based on a number of things above, it is necessary to do this research to determine the accuracy of drug use in terms of indications, drugs, patients, dosages and potential drug interactions and patterns of drug use in hepatitis B.

METHODS

This study was an observational study with a cross-sectional design. The data was taken retrospectively at the "X" hospital in Semarang, the material used was medical records. The data period used is January 2015-December 2016. The types of qualitative data include the type of drug and the dose given.

The sample size is based on the inclusion criteria. Subjects were patients with acute and chronic hepatitis B, with complications and non-complications. The inclusion criteria are patients aged 26-45 years old, undergoing laboratory examinations and receiving drugs, and complete medical record data. Exclusion criteria were patients with HBsAg non reactive laboratory examination results.

The variables in this study are the accuracy of the indication, drug, patient and dosage and the potential for drug interactions. To assess accuracy is done by recording the condition and drug data received by the patient, then matched with the literature. Evaluation of the potential for drug interactions is done by looking at the data of drugs that are used simultaneously, then matched with the literature. Explanation to evaluation results is carried out descriptively, referring to the libraries used. The results of the conformity assessment with the literature and

accuracy are expressed in percent. This research was conducted without meeting patients, so there were no ethical tests or requests for informed consent.

RESULTS

A total of 61 patient data met the inclusion criteria, the description data of the use of hepatitis B drugs used in the hospital "X" can be seen in Table 1. The result in Table 1 shows that all patients received hepatoprotector curcuma, while antivirals were given telbivudin (11.75% 0 and peginterferon α2 (9.8%).

In Table 2 shows the use of drugs based on patient diagnosis. There is a difference in drug administration given to hepatitis without complications with hepatitis + complications. The ones without complications are given at most 2 types of drugs, while with complications at least 2 types of drugs are given.

The data obtained are then evaluated for the accuracy of the indications, drugs, patients, and doses where the results of the evaluation of accuracy can be seen in Table 3. Four kinds of drugs are given in cases of hepatitis, curcuma drugs, ursodeoxycholic acid, and peginterferon α2 exactly 100% for indication, medication, patient, and dosage. A drug, telbivudin, medicine, patient, and a dose of 100%, while the exact indication is 82%.

The data shown in Table 4 shows the potential occurrence of drug interactions, namely drugs taken simultaneously by the patient. There are 3 cases (4.92%) giving 2 kinds of drugs that are given simultaneously (Peginterferon alfa 2a with ondansetron) which has the potential to cause interaction.

DISCUSSION

Overview of drug use

All patients (100%) received the curcuma hepatoprotector drug, while the Wenge (2009) study showed 81% of patients received hepatoprotector (curcuma 9.5%) and in the Trisnaningtyas (2017) study patients who received hepatoprotector were 33.52% (curcuma 17 , 88%). The difference in the percentage of curcuma administration in this study is different from the previous study because the research sites were different hospitals and cities.

Hepatoprotector administration in hepatitis B patients is intended to restore liver function to improve again so that the liver parameter values, one of which is ALT / AST, returns to normal. (6) The administration of curcuma as a hepatoprotector is intended to prevent liver cell damage. (7) Based on research, curcuma can inhibit hepatitis B virus infection (8)
Distribution of Ursodeoxycholic acid in hepatitis B patients, due to Ursodeoxycholic acid significantly reduces the risk of hepatitis B antigen positivity (HBsAg) and serum DNA level

of hepatitis B virus. Ursodeoxycholic acid significantly reduces the risk of an increase in abnormal serum transaminase activity in chronic hepatitis B. (9) The provision of pegylated interferon alpha antiviral namely alpha 2-a interferon in hepatitis B patients aims to increase the host immune response to fight hepatitis B virus and inhibit hepatitis B virus replication. (10) In the studies conducted by Wenge (2009) and Trisnaningtyas (2017) there were no patients who were prescribed the drug.

Distribution of nucleoside analogues in hepatitis B patients due to nucleoside analogues effectively suppresses the level of DNA of hepatitis B virus. (5) Telbivudin is one of the nucleoside analog class drugs that function in inhibiting hepatitis B virus replication (11). The evaluation results of the use of hepatitis drugs were 100% of patients with hepatoprotector curcuma administration, and 81.97% of antiviral drugs. Therapy given is in accordance with the PPHI (2009) guideline, including the exact drug and dosage of 100%. Indications of curcuma administration in accordance with the Indonesian Depkes RI (2008) are exactly 100%, while indications of antiviral administration based on PPHI are exactly 82%.

Overview of drug use based on disease diagnosis

Based on the results of hepatoprotective combination treatment and antiviral drugs compared non-hepatoprotective antiviral drugs in hepatitis B patients showed that combination therapy of hepatoprotective agents and antiviral drugs was more effective than anti-hepatoprotective antiviral drugs to reduce liver cell damage and the use of two hepatoprotective agents was better than hepatoprotective agents single in normalizing aminotransferase (ALT) levels and the amount of bilirubin in hepatitis B patients (12)

As a comparison for the evaluation of therapy for hepatitis B patients at Dr. Sardjito Hospital Yogyakarta in 2012-2014, the antiviral drugs used were entecavir by 4%, lamivudin by 88%, and tenofovir by 8%. Supporting therapies used in hepatitis B therapy as hepatoprotectors were curcuma at 17.88%, SNMC at 8.38%, and HP Pro at 7.26%. (6) Based on studies of the characteristics and use of drugs in patients with hepatitis B in Manado City Government Hospital for the period January 2011-December 2012, the drug for hepatitis B treatment used was hepamax by 38.6%, curcuma by 30%, pro liver by 1.4 %, sebivo by 5.7%, lamivudin by 1.4%, HP Pro by 5.7%, lesichol 300 by 1.4%, HP Pro + hepamax by 5.7%, curcuma + hepamax by 12.9% , and hepamax + sebivo at 1.4%. (13) So, there are differences in the delivery of hepatitis B drugs to hepatitis B patients in each of these hospitals.

Appropriate evaluation of indications

Patients with hepatitis B virus infection can be given hepatic protector drugs and cholelitolytic drugs. (14) Curcuma can be indicated in patients with hepatitis B because it has an antioxidant effect by capturing superoxide ions and breaking the chain between superoxide ions so as to prevent liver cell damage. (7) Curcuma can inhibit hepatitis B virus infection by inhibiting histone acetylation of hepatitis B virus-cccDNA bonds which results in the positivity of hepatitis B surface antigen (HBsAg) and reduced activity of hepatitis B virus (HBeAg) so that

hepatitis B virus replication is inhibited. (8) Ursodeoxycholic acid can be indicated in hepatitis B patients because it can reduce ALT levels in hepatitis B patients (12) by increasing the transport of bile acids and / or detoxification, cytoprotection and anti-apoptotic effects. (15)

In the literature referred to from (16, 17, 14) does not explain the handling of hepatitis B patients with hepatocellular carcinoma (hepatoma). However, in the research journal it was explained that hepatitis B patients accompanied by hepatocellular carcinoma should be considered for the provision of antiviral therapy in order to prevent tumor recurrence or prevent liver decompensation. (18)

Appropriate evaluation of drugs

(14) Curcuma has the effect of being an antioxidant capable of capturing superoxide ions and breaking the chain between superoxide ions, thus preventing liver cell damage. (7) Based on curcuma research, it can inhibit hepatitis B virus infection by inhibiting histone acetylation of hepatitis B virus-cccDNA bonds which results in the positivity of hepatitis B surface antigen (HBsAg) and decreased activity of hepatitis B virus (HBeAg) so that hepatitis B virus replication is inhibited. (8) The administration of hepatoprotectors in hepatitis B patients is intended to restore the liver's function so that it returns to recovery so that the liver parameter values, one of which ALT / AST can also return to normal. (6)

Ursodeoxycholic acid is clinically included in hepatoprotector agents, can be indicated in hepatitis B patients because it can reduce ALT levels in hepatitis B patients (12) by increasing the transport of bile acids and / or detoxification, cytoprotection and anti-apoptotic effects. (15) Based on Ursodeoxycholic acid studies significantly reduce the risk of hepatitis B surface antigen positivity (HBsAg) and hepatitis B virus serum DNA levels for acute hepatitis B and ursodeoxycholic acid significantly reduce the risk of increased abnormal serum transaminase activity in chronic hepatitis B. (9)

Nucleoside analogues can be given to hepatitis B patients, nucleoside analogues effectively suppress hepatitis B virus DNA levels. (5) Telbivudin functions in inhibiting hepatitis B virus replication. from ALT normalization. (19) In a comparative study of telbivudin and entecavir, both drugs provided the same potential in normalizing ALT and suppressing the hepatitis B virus DNA in short-term therapy. In the case of HBeAg telbivudin clearance is superior to entecavir (20) In another study it was also found that the administration of telbivudin was superior to adefovir in suppressing the hepatitis B virus DNA until it was not detected. (16)

As many as 100% of patients receiving alpha 2-a interferon injections are right for the drug. Pegylated interferon alpha has a dual mechanism of action as an immunomodulator in which pegylated interferon alpha activates macrophages, natural killer cells (NK) and cytotoxic T lymphocytes and modulates the formation of antibodies that will enhance the host's immune response to fight hepatitis B virus and as antiviral activity by inhibiting the replication of hepatitis B virus directly through activation of endo-ribonuclease, elevation of protein kinase

and induction of 2 ', 5'-oligodenylate synthetase. (10) Pegylated interferon is available in 2 types, namely pegylated-interferon α-2a (Peg-IFN α-2a) and pegylated-interferon α-2b (Peg-IFN α-2b), based on research there are no significant differences in the use of Peg-IFN α -2a and Peg-IFN α-2b in the inhibition of hepatitis B virus replication. (21) At this time what has been accepted as a drug for hepatitis B is pegylated interferon α-2a. (10)

Appropriate patient evaluation

Curcuma is contraindicated in patients with hypersensitivity to curcuma. (26) Ursodeoxycholic acid is contraindicated in patients with hypersensitivity to Ursodeoxycholic acid. (26) In all patients there is information that there is no history of allergy to the drug.

Telbivudin is contraindicated in patients with hypersensitivity with telbivudin. (22) Interferon is contra-indicated in patients with psychiatric disorders, women who are pregnant, active autoimmune diseases. (16) Interferon alpha 2-a is also contraindicated in patients with hypersensitivity to active substances (alpha-interferon) and excipients. (23) In this study all patients had no history of allergy to the drug.

Appropriate dosage evaluation

Maximum safety indication of curcumin dose is 12g / day with 3 months treatment duration. (24) The administration of Curcuma 20 mg 3 times daily in all patients did not exceed the maximum safety indication limit of dose.

Ursodeoxycholic acid dosage range for hepatitis B virus therapy ranges from 150–900mg / day with treatment duration ranging from 3 weeks to 2 years. (25) Administration of Ursodeoxycholic acid of 250 mg 3 times daily in patients not exceeding the maximum dose limit.

Telbivudin dose is recommended at 600 mg / day. (16) duration of telbivudin administration for ≥52 weeks. (26) The administration of telbivudin for 600 mg 1x a day in patients was in accordance with the recommended dosage.

A total of 6 patients received alpha 2-a interferon for 180 μg by injection, 100% had the right dose, that is precisely the amount of drug given based on the dose received by the patient stated in the medical record compared to the literature. The dose of alpha 2-a interferonone is recommended at 180μg / week with the duration of administration of alpha 2-a interferon for 48 weeks. (10) 180 mg of alpha 2-a interferon in the patient is in accordance with the recommended dose.

The potential interactions occur are minor (harmless) between alpha 2-a and ondansetron interferoners where alpha 2-a interferon will increase the ondansetron effect by affecting the

hepatic enzyme metabolism CYP1A2. (27) Potential minor drug interactions have usually mild effects and may not require changes in therapy so that they can still be tolerated. (28)

Conclusion

The evaluation results of the use of hepatitis drugs were 100% of patients with hepatoprotector curcuma administration, and 81.97% of antiviral drugs. Therapy given is in accordance with the 2009 PPHI guideline, including the exact drug and dosage of 100%. Indications of curcuma administration in accordance with the Indonesian Ministry of Health (2008) are exactly 100%, while indications of antiviral administration based on PPHI are exactly 82%.

Hepatoprotector drug (Curcuma) is used by all hepatitis B patients, either as a single drug or in combination with other drugs, aimed at uncomplicated or complicated complications of hepatitis patients.

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ATTACHMENT. TABLE OF RESEARCH RESULTS DATA

Table 1. Overview of the use of hepatitis drugs based on drug categories

No	Drug category	Drug name	Number of patients receiving	
			n	%
1.	Hepatoprotector	Curcuma	61	100
		Ursodeoxycholic acid	49	80.33
2.	Antivirus	Telbivudin	9	11.75
		Peginterferon alfa 2a	6	9.8

Table 2. Overview of drug use in hepatitis patients undergoing hospitalization at "X" Hospital for the period January 2015 - December 2016 based on diagnosis

No	Complications category	Diagnosis	Drug group	Drug name	Number of patients receiving	
					n	%
1	Without complications	Hepatitis B	Hepatoprotector	Curcuma	12	19.67
			Hepatoprotector + cholelitolytic	Curcuma + ursodeoxycholic acid	21	34.43
2	Hepatitis + complications	+ hepatoma	Hepatoprotector + cholelitolytic	Curcuma + ursodeoxycholic acid	5	8.20
		+ ascites	Hepatoprotector + cholelitolytic	Curcuma + Ursodeoxy cholic acid	5	8.20
		+ ascites + hepatoma	Hepatoprotector + cholelitolytic	Curcuma + Ursodeoxy cholic acid	3	4.92
		+ cirrhosis + ascites	Hepatoprotector + cholelitolytic+ antivirus	Curcuma + Ursodeoxy + telbivudin	5	8.20

		nucleoside analogues			
	+ jaundice	Hepatoprotector + cholelitolytic+ antivirus nucleoside analogues	Curcuma + Ursodeoxy + telbivudin	4	6.56
	+ cirrhosis	Hepatoprotector + cholelitolytic + antiviral alpha interferon	Curcuma + Ursodeoxycholic acid + injection of peginterferon alfa 2a	4	6.56
	+ Cirrhosis + Ascites	Hepatoprotector + cholelitolytic + antiviral alpha interferon	Curcuma + Ursodeoxycholic acid + injection of peginterferon alfa 2a	2	3,28

Table 3. Description of percentage (%) accuracy of Indications, drugs, patients, and doses

No	Drug category	Drug name	Indication		Drug		Patient		Dose	
			acc urate	not	acc urate	not	acc urate	not	acc urate	not
1	Hepatoprotector	Curcuma	100	0	100	0	100	0	100	0
		Ursodeoxycholic acid	100	0	100	0	100	0	100	0
2	Antivirus	Telbivudin	82	18	100	0	100	0	100	0
		Peginterferon alfa 2a	100	0	100	0	100	0	100	0

Table 4. Overview of potential drug interactions

Drug name	Amount and percentage of events	
	n	%
Peginterferon alfa 2a with ondansetron	3	4.92

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