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Application Of Child - Turcotte Pugh Scale For The Assessment Of Severity Of Liver Dysfunction And Dosage Individualization

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Abstract: The hepatic metabolism and clearance of drugs are altered in liver dysfunction which necessitates the need for assessment of severity of liver dysfunction and dosage individualization. The degree of hepatic impairment was calculated using Child-Pugh classification and the dose adjustments were per formed using the published drug dosing guidelines. The dosing interval or the total dose was adjusted when necessary. The degree of liver function impairment of 50 patients was assessed in the present study. Among the 545 drugs prescribed, the dosages of 40 (7.33%) were adjusted based on the severity of liver dysfunction. Spironolactone, torsemide, and rabeprazole were some of the drugs for which dose was adjusted in patients with hepatic function impairment. Medication chart review and concurrent feedback by the clinical pharmacist may result in enhanced medication safety and improved therapeutic outcome in patients with hepatic dysfunction.

Keywords: liver dysfunction, Child-Pugh scale, hepatotoxic drugs, dosage adjustment.

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I. INTRODUCTION

Hepatic diseases are among the top ten killer diseases in India[1].According to the WHO data published in May 2017, death due to liver diseases in India has reached 259,749 people or 2.95% of the total deaths[2].In India, nearly 2lakh people die owing to terminal liver diseases, of these, 25,000 lives can be saved by transplants every year. Alcohol abuse, viral hepatitis, obesity and sedentary lifestyle are the most common risk factors in the development of liver dysfunction[3].

Liver dysfunction shows reduction in the clearance of drugs that are eliminated by hepatic metabolism .It also affects plasma protein binding, hence influences the distribution and elimination. In patients with liver diseases, the hepatic metabolic activity of the enzymes is also reduced[4].Dose adjustment in liver failure is especially critical because the accumulation of parent compounds or active metabolites can cause additional morbidity and costs. FDA guidelines recommend categorizing the patients by Child-Pugh classification, a semi-quantitative score that is used commonly in the assessment of severity of hepatic impairment[4]. It evaluates the synthetic liver function and helps in making adequate dosage adjustments in patients with hepatic impairment[5].

Prescribing drugs in patients with liver disease is a challenging task since there are no clear tests that can identify the altered drug metabolism. As illustrated by the earlier studies, dose of medications should be individualized depending on the need and alternatives available. In patients with severe liver failure, macrolide antibiotics like erythromycin and azithromycin are avoided due to impaired hepatic clearance, while the dose of metronidazole is reduced by 50%[6].The dosage individualization can maximize therapeutic efficacy and minimize the adverse drug reactions. Literature reveals that only a few studies have used Child -Turcotte Pugh Scale for the assessment of severity of liver dysfunction and dosage adjustments in hepatic impairment.

II. OBJECTIVES

The aim of the present study was to assess the severity of liver dysfunction in patients with liver function impairment using Child - Turcotte Pugh scale and to understand dosage individualization in selected patients with hepatic insufficiency.

III. MATERIAL AND METHODS

A prospective descriptive study was performed in the Gastroenterology department of a 750 bedded multispecialty tertiary care private corporate hospital for a period of 7 months from March to September 2017. The study protocol was approved by the Institutional Review Board (SRH/EC.9-13/2017-18). Patients having atleast one elevated value of basic liver function tests, receiving atleast one pharmacologically active drug and

willing to participate were included in the study. Laboratory data and clinical evaluation report of the physician were used as the source of information. Both verbal and written consent was obtained from each subject before initiating the study. The clinical and demographic details of the patient were collected using a structured proforma which includes age, gender, length of hospital stay, diagnosis, serum albumin, total bilirubin, alkaline phosphatase, SGPT levels, serum creatinine, International Normalised Ratio (INR) and prothrombin time. Prescribed drugs with dosage, frequency, and route of administration were also collected.

Using the Child-Pugh classification the degree of hepatic impairment was calculated which includes five variables: total bilirubin, serum albumin, prothrombin time, the presence of encephalopathy and the presence of ascites. Based on the score obtained disease severity was then classified as mild (class A), moderate (class B) or severe (class C).

Child-Pugh Classification of Severity of Liver Dysfunction			
Disease Parameter	***Points assigned***		
MEASURE	***1 POINT***	***2 POINT***	***3 POINT***
Total bilirubin(mg/dl)	<2	2-3	>3
Serum Albumin(g/dl)	>3.5	2.8-3.5	<2.8
Prothrombin time(Sec)	<4	4-6	<6
Ascites	None	Slight	Moderate
Encephalopathy	None	Slight	Moderate

A total score of 5 to 6 is considered Grade A (well-compensated disease); 7-9 is Grade B (significant functional compromise); and 10 to 15 is Grade C (decompensated disease)[2,6]

Hepatic encephalopathy is the occurrence of confusion, altered level of consciousness, and coma as a result of liver failure. The following table was used to determine the grade of hepatic encephalopathy[7].

The Severity of Hepatic Encephalopathy	
GRADE	***SYMPTOMS***
Grade 1	Trivial lack of awareness, euphoria or anxiety, shortened attention span, impaired performance of addition or subtraction.
Grade 2	Lethargy or apathy, minimal disorientation for time or place; subtle personality change, inappropriate behaviour.
Grade 3	Somnolence to semistupor, but responsive to verbal stimuli, confusion, gross disorientation.
Grade 4	Coma (unresponsive to verbal or noxious stimuli)

The dosing interval was increased or the total dose was reduced for those drugs with a potential to cause hepatotoxicity, high hepatic extraction ratio (ER>0.7) or drugs witha narrow therapeutic index using published drug dosing guidelines.

IV. RESULT

The mean age of the study population was 53.08yrs ± 16.44 (range 13 to 84yrs) with 70% male patients. Demographic details of these patients are shown in table1. Most of the patients were in adulthood (26%) followed by late adulthood (42%).

TABLE 1: DEMOGRAPHIC DATA

S.No	Parameters	Values (%)
1	N	50
2	Mean age(yrs)	53±16.44
3	Male	35
4	Female	15
5	Alcoholic	16
6	Smoker	13
7	Mean International Normalised Ratio	1.128±0.755
8	Mean serum creatinine(mg%)	1.044±1.115

9	Mean total bilirubin(mg%)	5.546±5.558
10	Mean serum albumin(g/dl)	2.938±0.654
11	Mean prothrombin time(Sec)	19.18±6.45
12	Mean alkaline phosphatase(U/L)	209.90±257.82
13	Mean SGPT(U/L)	156.8±289.88

The major diagnoses were liver cirrhosis (31.1%), alcoholic liver disease (16.3%) and jaundice (13.1%). About 70% of patients had multiple co-morbidities. A total of 545 drugs were evaluated in 50 patients in the present study. The mean number of drugs per patient was 10.90±3.60 (range 4-22). The major drug category prescribed were antibiotics (14.49%), vitamins and minerals (12.02%) and anti-ulcer drugs (10.82%).Drugs with high hepatic extraction ratio such as lactitol (28.12%), lactulose (25%) and sucralfate (12.5%) were also observed. Drugs prescribed with either adjusted dose or altered frequency of administration or both are summarized in table 2. These drugs belong to therapeutic categories such as diuretics (57.5%), antiulcer drugs (17.5%), antiemetics (10%), antibiotics (7.5%), antihypertensives (2.5%), antiasthmatics (2.5%) and antiepileptics (2.5%).

TABLE 2: PRESCRIBED DRUGS WITH ADJUSTED DOSAGES (N=40)

S.No.	Drugs prescribed	Normal dose	No.	%	Adjusted dose	Altered frequency of administration
1.	Spironolactone	25mg/50mg OD/BD	12	23.52	100mg	Once daily
2.	Torsemide	20mg OD	8	15.68	10mg	Once daily
3.	Rabeprazole	20mg BD	7	13.72	20mg	Once daily
4.	Ondansetron	4 mg TDS	4	7.84	8mg	Once daily
5.	Furosemide	20mg OD	3	5.88	40mg	Once daily
6.	Metronidazole	500mg TDS	2	3.92	500 mg	Once daily
7.	Doxophylline	400 mg BD	1	1.96	200 mg	Once daily
8.	Cefoperazone	4 g BD	1	1.96	4 g	Once daily
9.	Telmisartan +amlodipine	40mg+5 mg OD	1	1.96	40mg+2.5mg	Once daily
10.	Levetiracetam	500 mg BD	1	1.96	250 mg	Once daily

Drugs such as paracetamol, domperidone, metformin, and atorvastatin were carefully avoided in the study subjects. Narrow therapeutic index drugs such as clindamycin (6%) theophylline (2%) and warfarin (2%) were prescribed in 5 (10%) patients after considering risk and benefits.The severity of hepatic impairment of study population according to Child-Pugh classification is shown in table 3.

TABLE 3: SEVERITY OF HEPATIC IMPAIRMENT ACCORDING TO CHILD–PUGH CLASSIFICATION (N=50)

Severity	Child-Pugh Score	No. of patients	Percentage (%)
GRADE A	5-6	8	16
GRADE B	7-9	26	52
GRADE C	10-15	16	32

V. DISCUSSION

Liver disease is frequently associated with changes in the pharmacokinetic disposition of drugs that undergo metabolism[8]. Hence the choice of drug, its dose and duration of therapy must be carefully considered in order to avoid adverse effects [9].The usual adult dose of rabeprazole, a proton pump inhibitor is 20mg twice daily. However, in liver disease the half-life of this drug is increased 2-3 fold; hence once daily dose is recommended[10]. Torsemide is a loop diuretic prescribed at a dose of 20 mg OD in patients with normal liver function. Friedel et al. recommended that the initial dose in edema associated with hepatic cirrhosis is 5 mg or 10 mg orally once daily. Along with dose reduction, an addition of a potassium- sparing diuretic or aldosterone antagonist helps to prevent electrolyte imbalance leading to hepatic coma[11]. Furosemide is another loop diuretic widely used to treat edematous stage in the liver disease. The normal dose is 20 mg OD. Qureshi et al. reported that the natriuretic effect of furosemide is proportional to its renal concentration and the renal clearance is limited in cirrhosis, thus reducing the efficacy of the drug. Hence it is recommended to initiate the furosemide therapy with 40 mg/day for cirrhotic patients[12, 13].

Spironolactone, a potassium- sparing diuretic has been prescribed with a dose of 25mg BD and 50 mg OD. Increased plasma concentration of aldosterone is seen in cirrhosis with ascites which results in decreased sodium excretion[12]. Hence, an increased dose of spironolactone is required to obtain adequate natriuresis. Pedersen et al.(2015) suggested giving spironolactone in hepatic insufficiency at a dose of 100-200mg OD and maintenance upto 400mg OD[14].

A fixed dose combination of telmisartan and amlodipine (40mg+5mg) has been used for treating hypertension. In patients with impaired hepatic function the elimination half- life of amlodipine is 56 hours. Hence in hepatic impairment initial therapy with fixed dose combination is not recommended; as an initial dose start or add amlodipine 2.5mg to telmisartan and titrate slowly to clinical effect[15].

Paracetamol is metabolized by the liver, producing a nontoxic metabolite. In hepatic impairment altered metabolism and depleted glutathione stores results in accumulation of the hepatotoxic intermediate, N-Acetyl–P-benzo Quinone Imine (NAPQI). Hence it is contraindicated in severe hepatic impairment. Amarapurkur (2011) recommended that a dose less than 2gram per day is a safer option. In case of inadequate pain relief, tramadol 25 mg every 8 hrs can be used.[6]

Metronidazole is normally prescribed at a dose of 500mg TID. Amarapurkar recommended a reduction in the dose of metronidazole by 50% in hepatic impairment to avoid accumulation of metronidazole and it's metabolite.[6] The serum half-life of cefoperazone a third-generation cephalosporin is increased 2-4 fold in patients with hepatic disease or biliary obstruction[16]. Hence total daily dosage of greater than 4g is not recommended in hepatic disease.

The half- life of ondansetron is prolonged from 3-6.2 hrs to 11.6-20 hrs in hepatic impairment. Hence, a reduction in dose of ondansetron to 8 mg per day is recommended in severe hepatic impairment[17].Domperidone is contraindicated in moderate to severe hepatic impairment due to the prolonged half-life of 15 – 23 hrs[18].The plasma half-life of domperidone in patients with normal hepatic function is 7-9 hrs.

The ability to clear lactate is impaired in hepatic dysfunction, leading to lactic acidosis. Hence, the use of metformin is contraindicated in liver disease[19].Statins are reported to be safe in patients with stable or compensated liver cirrhosis. Its use is limited in decompensated cirrhosis and acute liver failure in view of elevation in liver biochemical parameters[21].Levetiracetam is an anti-epileptic prescribed at a dose of 500 mg BD. Ahmed et al. state that in patients with cirrhosis, total clearance of levetiracetam was reduced by 57%. Hence the reduction in dose by 50% is recommended[22].The half-life of doxofylline, a xanthine derivative is prolonged in patients with liver disease; hence a reduction of the dose is recommended[23].

Warfarin is a drug with a narrow therapeutic index. The liver is responsible for the synthesis of plasma clotting factor as well as the metabolism of warfarin. Hence active hepatic disease enhances the response to warfarin[24]. Brandl et al. state that the serum concentration of clindamycin which is primarily metabolized by the liver may be increased and the half-life prolonged to 5-15 hours in patients with cirrhosis[25]. Theophylline is another narrow therapeutic index drug with a therapeutic range of 5-15mcg/ml. Its clearance is decreased by 50% or more in patients with hepatic insufficiency[26]. The normal half-life in an adult is 6.1-12.8hrs which is prolonged to 32hrs in cirrhosis. Hence dose reduction and monitoring of serum theophylline concentration are required in patients with reduced hepatic function.

VI. CONCLUSION

Child-Turcotte Pugh Scoring served as a cornerstone in the evaluation of the degree of hepatic impairment and drug dosage adjustment in the current study. Of the 545 drugs evaluated, 40 (7.33%) required dosage adjustment. The current study observed that the prescribed drug dosage follows the recommended guidelines to a greater extent and are comparable with the existing literature.

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