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ROLE OF NON SPECIFIC LIVER DRUGS IN LIVER DISEASES; PRESCRIPTION HABITS OF THESE DRUGS AMONGST DOCTORS OF MULTAN CITY

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ABSTRACT

INTRODUCTION: In majority cases of liver disease, treatment is only symptomatic. Specific treatment is either not required (acute hepatitis) or not available (end stage liver disease). Taking advantage of the situations, a number of products are marketed in Pakistan claiming benefits in these situations (e.g., Hepalex, HepaMerz, Litrison). We will use the term "Liver drugs" for these products in this paper. **OBJECTIVES:** To find out facts about contents of these liver drugs in the literature and assess the validity of manufacturer's claims or to know that what percentage of doctors of Multan City prescribe these drugs, reasons for their prescription and source of knowledge influencing their decisions. **MATERIAL & METHODS:** A literature search was conducted to find out role of contents of these liver drugs, a survey was carried out among doctors of Multan city using a questionnaire, which was delivered and then collected at a later date. Questions were about prescription habits, reasons in support of prescription and sources of knowledge. **RESULTS:** There was no evidence in the literature suggesting any established beneficial role of any of the contents of these liver drugs in liver disorders. More than 80% doctors surveyed including GPs and Specialists were prescribing these drugs. Two common reasons given by these doctors in support of prescription were; that these products have favorable effect on the disease process and something had to be prescribed for the satisfaction of the patients and relatives. Main source of information about these drugs was pharmaceutical visits and literature provided by them. **CONCLUSION:** These non specific liver drugs have no established role in liver disorders but more than 80% doctors of Multan city are prescribing due to misconception created by the manufacturers that these drugs are beneficial.

KEY WORDS: Liver drugs, non specific, prescription habits.

INTRODUCTION

Liver diseases, both acute and chronic remain a major health problem worldwide and more so in Pakistan.

Majority of the patient of acute hepatitis recover spontaneously while chronic liver disease is usually progressive and no effective remedy is available to change the course of the disease except in certain circumstances e.g. antiviral therapy in chronic viral hepatitis[1,2,3,4] and immunosuppressants in autoimmune hepatitis[5]; even in these conditions response rate is not 100%.

Liver transplant is expensive and only available to a small number of patients of acute hepatic failure or end stage liver disease. In acute hepatitis and in a majority of patients with chronic liver disease treatment is offered for symptoms or complications only.

Taking advantage from lack of availability of specific treatment, some pharmaceutical companies have marketed non specific drugs in this country for the treatment of liver diseases, both acute and chronic, claiming various benefits. We will use the term "liver drugs" for these products in this paper. These products include Epuram, Essentiale, Hepalex, Hepa-Merz, Jetepar, Levijon and Litrison.

Benefits mentioned in the inserts of these products include :

1 Reduce liver work load
2 Promote liver clearance of fat
3 Restoration to normal in acute viral hepatitis
4 Convert toxic ammonia into non-toxic urea
5 Promotes liver function and detoxification
6 Helps to Counteract degenerative changes in the parenchyma of the liver

Indications as given in the literature of these products are;

1 Jaundice
2 Acute and chronic hepatitis
3 Alcoholism
4 Liver cirrhosis
5 Hepatic encephalopathy
6 Drug toxicity
7 Industrial toxins
8 Food intoxication
9 Fatty liver
10 Cholecystitis and cholangitis
11 Biliary and hepatic dyspepsia
12 Gestoses
13 Recurrent gallstone
14 Radiation damage
15 Nephrotic syndrome
16 Asthenia
17 Physical and mental overwork.

We carried out literature search to validate claims of manufacturers of these drugs and conducted a survey to find out opinion of medical practitioners of Multan City about these products.

OBJECTIVES OF THE STUDY

This study has two parts;

1. Literature search to find out the facts about contents of co called "liver drugs".
2. Survey to find out:

a Whether GPs and specialists prescribe these drugs in liver disease patients.
b Preference for various products available
c Reasons for using or not using these agents
d Sources of knowledge influencing their decision-making.

MATERIAL & METHODS

Literature search was carried out using accessible sources including ;

- Journals and books of pharmacology, therapeutics and hepatology
- Product inserts
- Internet

Survey was conducted using a questionnaire (copy attached) which was distributed among GPs and specialists of Multan city. It was delivered and then collected at a later date personally.

RESULTS

LITERATURE SEARCH

The contents of various products are shown in table I. There is no role of any of these contents in any form of liver diseases. Only exception is role of L-ornithine L-aspartate in hepatic encephalopathy, which is still controversial (table II).

Table-I. Contents of products (liver drugs) as described in product inserts

Product	Contents
Epuram	L-arginine, L-ornithine, L-citruline
Essentiale	Essential phospholipids, vitamin B_6, B_{12}, nicotinamide, sodium-D-pantothenate
Hepalex	L-ornithine L-aspartate, nicotinamide, riboflavin, 5-phosphate sodium, vitamin B_1, B_6, B_{12}
Hepa-Merz	L-ornithine L-aspartate
Jetepar	Glucometamine, glucodiamine, nicotinamide
Levijon	L-ornithine L-aspartate, B-complex
Litrison	Methionine, choline tartrate, vitamins of B complex, vitamin E.

Table-II. Pharmacological effects of contents of liver drugs

Name of ingredient	Pharmacological effects
Vitamins	Nutrient
L-ornithine L-aspartate	Are amino acids, have been used to treat hyperammonaemia in hepatic encephalopathy[1,2]
Citruline	Is an amino acid used in the urea cycle. It has been used as a substitute for arginine in the treatment of inborn error of urea synthesis[2].
Choline chloride	Is an acetyl-choline precursor, involved in lipid metabolism. It has been considered a vitamin B substitute[2,3].
Methionine	Is chemically L 2-amino 4-butyric acid
L-arginine	It is an aliphatic amino acid. Have been used in the treatment of hepatic encephalopathy with no proven benefit.
Glucometamine and glucodiamine	These chemicals are not mentioned in the literature we searched except product insert which describes them as lipotropic and detoxicating agents
Essential phospholipid	Contains excess of unsaturated fatty acids, predominantly linoleic acid, linolenic acid and oleic acid. No benefit on liver diseases is mentioned in the literature.

SURVEY

A total of 136 doctors, 116 Gps and 20 specialists were surveyed. 111 (82%) doctors said they prescribe liver drugs. Percentage of GPs and specialists prescribing liver drugs was 89 (103 out of 116) and 40 (8 out of 20) respectively (table III).

When asked about preference of product, out of 103 GPs saying yes 89 (86%) gave their choice and 14 abstained while all the 8 (100%) specialists saying yes

gave their choice. Hepa-Merz and Jetepar were the two most popular liver drugs being preferred by more than 75% of those doctors who prescribed liver drugs, Litrison was preferred by one third of them while Bilsan, Epuram, Hepalex and Levijon were unpopular. Above mentioned products were nearly equally popular among specialists and GPs. Hepabionta was more popular among specialists compared with GPs (table IV).

Table-III. Frequency of liver drugs prescription

Prescription habit	GP n=116 (%age)	Specialist n=20 (%age)	Total n=136 (%age)
Prescribing drug	103 (89)	8 (40)	111 (82)

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Prescription habit	GP n=116 (%age)	Specialist n=20 (%age)	Total n=136 (%age)
Not prescribing drug	13 (11)	12 (60)	25 (18)

The doctors gave multiple reasons for prescribing drugs. Most common reason given by the GPs was that they reduce complications of liver disease followed by symptomatic relief and satisfaction of patient and relatives. Most common reason given by the specialists was patient/relatives satisfaction followed by symptomatic relief and reduction of complications. Percentage of GPs and specialist giving a particular reason was different but this difference was statistically insignificant except for the reason " Withholding drugs have deleterious effects on course of illness ($p< .0001$)" (table V).

Nearly all the doctors who were against prescribing liver drugs were of the opinion that these have no effect on illness and that to satisfy the patient / relatives. Counseling is better than prescribing nonspecific drugs. Half of these doctors said these drugs could even be harmful (table VI).

Table-IV. Preferences

Drug	GP n=89 (%age)	Specialist n=8 (%age)	P Value
Bilsan	7 (7.9)	-	.410
Epuram	-	-	-
Essentiale	40 (44.9)	2 (25)	.275
Hepabionta	27 (30.3)	5 (62.5)	.064
Hepalex	3 (3.4)	1 (12.5)	.214
Hepa-Merz	67 (75.3)	7 (87.5)	.436
Jetepar	66 (74.2)	6 (75)	.958
Levijon	13 (14.6)	-	.245
Litrison	23 (25.8)	3 (37.5)	.476

Table-V. Reasons of prescription

Reasons of prescription	Gps No (total) %age*	Specialists No (Total) %age*	P Value
Reverse disease process	20 (78) 25.6%	1(6) 16.7%	.625 NS
Halt progress of disease	30 (72) 41.7%	3 (6) 50%	.691 NS
Reduce complications	65 (97) 67%	4(7) 57.1%	.594 NS
Withholding drugs have deleterious effects	35(83) 42.2%	0(6) 0%	.0001 S
No effect on course of illness but provide symptomatic relief	58(98) 59.2%	5(8) 62.5%	
Are prescribed for patient / relatives satisfaction	49(94) 52.1%	4(6) 66.7%	.489 NS

* "No" is the number of doctors saying yes to the question; "total" is the total number of doctors answering the question; "%" is the percentage of doctors saying yes

Major source of information for both Gps and specialists was pharmaceutical visits. Expert's opinion and books were also important sources for both groups. Symposia was acknowledged as an important source of information by the Gps but not by the specialists. Journals and internet were accessible to minority (table VII).

Table-VI. Reason for non-prescription

Reasons of non- prescription	Gps No (total) %age*	Specialists No (Total) %age*	P Value
Drugs are unnecessary because of no effect on illness	12(13) 92.3%	11(12) 91.7%	.953 NS
Explaining to patient is better than prescribing for the sake of satisfaction	11(11) 100%	11(11) 100%	1.000
These drugs may be harmful	5(12) 41.7%	5(10) 50%	.696

Table-VII. Source of information

Source of information	Gps No (total) %age*	Specialists No (Total) %age*	P Value
Because experts use it	49(72) 68.1%	9(16) 56.3%	.368
Your books	42(75) 56%	8(16) 50%	.661
Pharmaceutical visits	78 (87) 89.7%	11(16) 68.8%	.025
Symposia	42(63) 66.7%	2(14) 14.3%	-
Do you receive any journal	30(80) 37.5%	4(16) 25%	.340
Do you have access to internet	14(84) 16.7%	2(16) 12.5%	.67

DISCUSSION

Liver diseases, both acute and chronic , are common and except in limited situations (e.g. chronic viral hepatitis B and C and acute hepatitis C) no specific drug treatment is available. They are either self-limiting e.g. majority cases of acute hepatitis or progressive e.g. most cases of advanced chronic liver disease.

As these diseases are potentially serious and can be fatal acutely (fulminant hepatic failure) or progress to end stage liver disease, both doctors and patients are genuinely concerned. Taking advantage of this situation a number of products (table I) have been marketed with exaggerated claims of unusual benefits in liver diseases as described under introduction.

Information obtained about contents of these drugs literature search using various sources including books, journals, internet and inserts of products is as follow.
Vitamins: these nutrients have nothing to do with progress or prognosis of liver diseases. L-Ornithine L-Aspartate: these are amino acids, have been used to treat hyperammonaemia in hepatic encephalopathy[7,9].

Results of these studies are conflicting but if we accept that these are useful in managing hepatic encephalopathy does not justify that these should be promoted for use in "all kind of liver diseases and more" as highlighted in the adds and commercial literature of the manufacturer. Citrullin: it is an amino acid used in the urea cycle. It has been used as a substitute for arginine in the treatment of inborn error of urea synthesis[7]. There is no reference regarding its role in any kind of liver disease. Choline chloride: it is an acetylcholine precursor involved in lipid metabolism. It has been considered a vitamin B substitute and has nothing to do with liver diseases[7,8].

Methionine: it is chemically L2-amino 4-butyric acid. We could not find any reference about its useful role in liver diseases. L-arginine : it is an aliphatic amino acid. It has been used in the treatment of hepatic encephalopathy with no proven benefit; otherwise it has nothing to do with prognosis of acute or chronic liver disorders.

Glucometamine and Glucodiamine: These chemicals are not mentioned in the literature we searched except

product insert which describes them as lipotropic and detoxicating agents, a false claim without any proof.

Essential phospholipids: These contain excess of unsaturated fatty acids, predominantly linoleic acid, linolenic acid and oleic acid. Their role in the liver diseases is not mentioned in the literature. As discussed above the contents of these liver drugs have no proven value in the treatment of liver diseases.

The survey conducted during this study has shown that more than 80% practitioners prescribe these drugs. Main reason given in the support of prescription is the misconception than they have favorable effect on the disease process and outcome, although some prescribe only for the satisfaction of the patients and relatives. This misconception is being created by the information provided by the pharmaceutical representatives and during symposia.

Arranged by the same for the promotion of their products. So decision-making process is being influenced by the incorrect information provided by the manufacturers. Regarding the question "if no proven effective treatment is available, should one prescribe drugs with false claims of benefit just for the satisfaction of the patient and relatives" our opinion is that if patients / relatives are properly explained, no one would like to spend money on drugs with no benefit.

CONCLUSIONS

There is no evidence of any benefit of these-so-called liver drugs" in liver diseases. Prescribing these drugs adds to the financial burden of patients. These are being prescribed by more than 80% medical practitioners under the influence of false information provided by the manufacturers.

RECOMMENDATIONS

Steps should be taken to make sure that true evidence based information is communicated to the professionals without any bias and exaggeration. Regulations are required to make sure that pharmaceutical industry can not spread false and misleading information through various means. Commercial literature of the pharmaceuticals including ads should be properly scrutinized before publication and distribution. Registration of these nonspecific "liver drugs" should be cancelled to prevent waste of public resources.

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