Clinical Efficacy of Lactulose in Cirrhotic Patients With and Without Subclinical Hepatic Encephalopathy

AKIHARU WATANABE,[1] TAKAHIRO SAKAI,[2] SHUNICHI SATO,[3] FUKASHI IMAI,[4] MASAO OHTO,[5] YASUYUKI ARAKAWA,[6] GOTARO TODA,[7] KENICHI KOBAYASHI,[8] YASUTOSHI MUTO,[9] TADASU TSUJII,[10] HIRONAKA KAWASAKI,[11] KIWAMU OKITA,[12] KYUICHI TANIKAWA,[13] SHIGETOSHI FUJIYAMA,[14] AND SHIGEHIKO SHIMADA[15]

Seventy-five cirrhotic patients with hyperammonemia in the past or at the time of the study were randomly divided into two groups (treated with lactulose or nontreated) in 14 hospitals in Japan. Thirty-six cirrhotic patients were diagnosed as having subclinical hepatic encephalopathy (SHE), and 39 were diagnosed as non-SHE. SHE was diagnosed when the results of all three of the quantitative psychometric tests used (number connection test, and symbol digit and block design tests of the Wechsler adult intelligence scale [revised]) were abnormal as compared with age-matched normal values. The mean number of abnormal psychometric test results and the prevalence of SHE were used for a quantitative evaluation of the efficacy of the lactulose treatment. Twenty-two of the SHE patients were treated with lactulose (45 mL/d) for 8 weeks, and the other 14 SHE patients did not receive lactulose. In the SHE patients administered lactulose, the results of the quantitative psychometric evaluation were significantly improved at 4 and 8 weeks after the beginning of the lactulose administration. The SHE had disappeared in 10 (50%) of the 20 treated patients at week 8, but it persisted in 11 (85%) of the untreated 13 patients. We concluded that lactulose treatment in cirrhotic patients with SHE is effective with respect to psychometric tests. (HEPATOLOGY 1997;26:1410-1414.)

Because the treatment for complications of cirrhosis such as hepatic encephalopathy, jaundice, ascites, and gastrointestinal bleeding has improved, the survival period of cirrhotic patients has been markedly prolonged. Therefore, an increasing number of patients with compensated or noncompensated cirrhosis are managed in outpatient clinics over a long period. In these patients, prevention of the above complications is necessary in long-term home care to improve the quality of life (QOL).

In hepatic encephalopathy, psychoneurological symptoms are clinically absent before the onset and during the interval period of encephalopathic episodes. However, subclinical hepatic encephalopathy (SHE), in which behavior abnormalities and impairment in cognitive functions can be shown by quantitative psychometric (neuropsychologic) tests, has been reported recently in cirrhotic patients who have no history of encephalopathy, and clinically appear to be free of encephalopathy.[1,2] Moreover, recent imaging analysis of the brain in cirrhotic patients with and without encephalopathy has shown brain atrophy on computed tomography,[3] abnormal regional cerebral blood flow on single photon emission computed tomography,[4] and high signals in the basal ganglia on T1-weighted magnetic resonance imaging.[5]

Therefore, it is important for the long-term management of cirrhotic patients to understand the presence of these morphological changes and functional impairments of the brain, and to pay attention to changes in daily behavior and sleep. This approach would be useful for maintaining the compensated stage of cirrhosis over a long period and for reversing the noncompensated cirrhosis to compensated cirrhosis.

Lactulose has been used worldwide for the treatment of hepatic encephalopathy since 1966,[6] and is a basic treatment for the disease along with a low-protein diet. However, the usefulness of lactulose has been studied primarily in patients with overt hepatic encephalopathy.[7,8]

In the present study, we examined whether lactulose administration at a conventional dose was beneficial in cirrhotic patients from 14 hospitals in Japan who had no overt encephalopathy but showed hyperammonemia in the past or at the time of the study. SHE in the patients was examined with three psychometric (neuropsychological) tests, and the clinical findings were serially compared between those administered and those not administered lactulose.

PATIENTS AND METHODS

Cirrhotic Patients. The subjects were 90 inpatients or outpatients who showed hyperammonemia in the past or at the time of the study, but were considered clinically to have no overt encephalopathy accompanied by psychoneurological disorders. The diagnosis of cirrhosis was made histologically or clinically. Patients with a history of overt encephalopathy and those with hepatocellular carcinoma that was considered to have no major effect on the clinical findings were included in the present study. However, the following patients were excluded from the study: those who had definite

Abbreviations: QOL, quality of life; SHE, subclinical hepatic encephalopathy; EEG, electroencephalogram.

From the [1]Third Department of Internal Medicine, Toyama Medical and Pharmaceutical University, Toyama; [2]Department of Internal Medicine, Saga Medical School, Saga; [3]First Department of Internal Medicine, Iwate Medical University, Morioka; [4]Department of Internal Medicine, Social Insurance Omiya General Hospital, Omiya; [5]First Department of Internal Medicine, Chiba University School of Medicine, Chiba; [6]Third Department of Internal Medicine, Nihon University, School of Medicine, Tokyo; [7]First Department of Internal Medicine, The Jikei University School of Medicine, Tokyo; [8]First Department of Internal Medicine, School of Medicine, Kanazawa University, Kanazawa; [9]First Department of Internal Medicine, University School of Medicine, Gifu; [10]Third Department of Internal Medicine, Nara Medical University, Kashihara; [11]Second Department of Internal Medicine, Faculty of Medicine, Tottori University, Yonago; [12]First Department of Internal Medicine, Yamaguchi University, School of Medicine, Ube; [13]Second Department of Internal Medicine, Kurume University, School of Medicine, Kurume; [14]Third Department of Internal Medicine, Kumamoto University School of Medicine, Kumamoto; and [15]Department of Pharmacy, Kitasato University Hospital, Sagamihara, Japan.

Received December 28, 1996; accepted July 23, 1997.

Address reprint requests to: Akiharu Watanabe, M.D., Third Department of Internal Medicine, Faculty of Medicine, Toyama Medical and Pharmaceutical University, 2630 Sugitani, Toyama, 930-01 Japan. Fax: 81-0764-34-5027.

0270-9139/97/2606-0007$3.00/0

TABLE 1. Prevalence of Abnormal Psychometric Tests and Hyperammonemia in 75 Cirrhotic Patients Without Overt Hepatic Encephalopathy

	Normal Values*	% Abnormal
Number connection test (sec)	≤40	65
Symbol digit test (gross points)	≥46	71
Block design test (gross points)	≥38	69
Abnormal results on all three tests		48
Hyperammonemia†		79

* Obtained from data collected from 102 age-matched control subjects (see text).

† Hyperammonemia was diagnosed in each hospital based on venous blood ammonia levels (before breakfast) being above the upper limit of the normal range (usually determined by an enzymatic or diffusion method). Seventy-nine percent of the patients showed hyperammonemia at the time of the study, and other patients had a history of hyperammonemia.

hepatic encephalopathy with grade II or more advanced encephalopathy (grades III to IV) at the beginning of the study; those with severe hepatic disorders whose serum total bilirubin level was 5 mg/dL or higher; those who were scheduled to be treated for esophageal varices during the study period; and those with severe gastrointestinal disorders such as diarrhea, bleeding, and acute abdomen. Patients likely to have difficulties performing the psychometric tests, such as those with neurological diseases or bad vision, were also excluded from the study.

Of the 90 patients initially registered, 15 were excluded, because 5 did not come to the hospital during the observation period before the beginning of the study (lost cases), 5 met the exclusion criteria (e.g., serum total bilirubin concentration ≥ 5 mg/dL; excluded cases), 3 stopped coming to the hospital after the beginning of the study (dropouts), and 2 used prohibited drugs during the study period and were considered impossible to assess. As a result, 75 patients (age, 60 ± 8 [32-75] years), of whom 41 were administered lactulose and 34 were not, were analyzable. The envelope randomization method was used to assign the patients to the lactulose and nonlactulose groups, as described below. The clinical backgrounds of the two groups (lactulose/nonlactulose) showed no significant differences between them in the age (60 ± 9/62 ± 8 years), sex (M:F: 26:15/15:19), incidences of Child-Pugh grades[9] (A:B:C, 23:11:7/20:12:2), and cirrhosis types (HBV:HCV:alcohol:others, 4:26:7:4/4:23:1:6).

Informed consent was obtained from all subjects in the present study.

Neuropsychologic Assessment. The diagnosis of SHE was made by quantitative psychometric tests that included the number connection test (trailmaking test A), and two performance subtests of the Wechsler adult intelligence scale (revised)(WAIS-R), symbol digit, and block design tests. The detailed methods and clinical significance of the three tests are described in our previous reports.[10-12] All of the test results were assessed according to the normal values of age-matched data collected from 102 control subjects. Abnormalities in the results of all three psychometric tests (values outside the mean ± 2 SD for the control subjects) were considered to be indicative of SHE (Table 1). The control subjects for the psychometric tests included 82 healthy volunteers and 20 inpatients without liver dysfunction or psychoneurological disorders (intestinal, lung, and renal diseases; thyroid and other endocrinological diseases), whose age was 61 ± 7 (40-70) years. The control subjects were 46 men and 56 women.

As a result, the diagnosis of SHE was made in 36 (48%, SHE group) and not in the remaining 39 (52%, non-SHE group) of the 75 assessable patients. The attending physicians did not know whether or not their patients had SHE during the study.

Methods for Clinical Trial. The controller (Dr. S. Shimada) put cards indicating lactulose administration or no treatment into randomization envelopes, sealed them, and numbered them. Five patients from each of the two groups were regarded as a batch, and each batch of 10 patients was randomly assigned to the lactulose administration or no-treatment group. When a cirrhotic patient who was considered to fit the selection criteria for this study was encountered, the next available randomization envelope was unsealed according to the serial number, and the treatment indicated by the card inside was performed. When the card indicated no treatment, no drug (lactulose or substitute) was administered. When the card indicated lactulose administration, lactulose syrup (60%; Nikken Chemicals Co., Tokyo, Japan) was orally administered at 45 mL/d (two to three times per day). When changes in the dose were necessary, the dose was kept in the range of 30 to 60 mL/d as much as possible so that bowel movements could be maintained at two to three times per day. The mean doses of lactulose 4 weeks and 8 weeks after the beginning of the administration were 42 ± 11 and 44 ± 11 mL/d, respectively.

Lactulose was administered for 8 weeks (study period) after a 2-week observation period (wash-out period). Because the blood ammonia concentration was high in many patients in the present study, basic treatments for hyperammonemia such as a low-protein diet (40 g protein per day on average) for inpatients and low-protein diet guidance for outpatients were performed. The contents of the diet were made as constant as possible throughout the study period.

Concomitant medications (including drugs used for the treatment of complications of cirrhosis or conditions other than cirrhosis) were continued with minimal changes in the dose, but the use of drugs that were considered to have direct effects on hepatic encephalopathy, such as branched-chain amino acid preparations and nonabsorbable antibiotics, was prohibited in principle. Therefore, in patients administered these agents before the test, these were discontinued in the wash-out period.

Urine and feces, subjective symptoms (e.g., malaise, feeling of abdominal distention, upper abdominal pain, anorexia, heartburn, nausea, vomiting, and sleep disorders), nutritional state, blood biochemistry, blood ammonia concentration, and the number connection test and Wechsler adult intelligence scale (revised) were examined by the routine methods[10-12] immediately before the beginning of the study, and at 4 and 8 weeks after the beginning of lactulose administration.

For the quantitative evaluation of the efficacy of lactulose, the results of the above three psychometric tests were evaluated according to the mean number of abnormal psychometric test results and the prevalence of SHE.

In the lactulose-treated group, the drug compliance was examined, and, if side effects were observed, the symptoms, dates of their appearance, their severity, treatments, outcome, and relationship with the lactulose administration were evaluated.

Follow-up Study. The patients were examined 6 months after the end of the study period with regard to the condition of lactulose administration, subjective symptoms, occurrence of overt hepatic encephalopathy, and nutritional state. These clinical findings—including whether the lactulose administration was continued, discontinued, still not administered, or started—were checked in 62 patients with and without SHE during the study period.

Statistical Analysis. The results are expressed as the mean ± SD, and statistical analyses were performed by the *t* test (one-sample, two-sample), Wilcoxon test, and χ^2 test. $P < .05$ was considered significant.

RESULTS

Concerning the clinical characteristics, significant differences between the SHE and non-SHE groups were observed in the number of abnormal psychometric test results, but not in the sex, inpatient/outpatient state, cause and severity of cirrhosis, duration of illness, complications (esophageal vari-

TABLE 2. Clinical Characteristics of SHE Patients (S) and Non-SHE Patients (NS) Administered (L) and Not Administered (NL) Lactulose

	Group S-L (n = 22)	Group S-NL (n = 14)	Group NS-L (n = 19)	Group NS-NL (n = 20)	P
Age					
Mean	62.0 ± 7.3	65.6 ± 7.1	56.7 ± 9.5	58.6 ± 6.2	*
<60 years	10	3	9	10	NS
≥60 years	12	11	10	10	
Sex					
Male	12	5	14	10	NS
Female	10	9	5	10	
Body weight (kg)	59.1 ± 11.0	53.4 ± 8.0	62.3 ± 12.4	59.3 ± 8.7	NS
Diagnosis and Etiology					
Cirrhosis	14	8	16	11	
Cirrhosis complicated by HCC	8	6	2	8	
Primary biliary cirrhosis	0	0	1	1	
HBV	1	2	3	2	NS
HCV	15	10	11	13	
Alcohol	4	0	3	1	
Others	2	2	2	4	
Duration of illness					
<5 years	5	3	2	4	
≥5 years	6	3	4	1	NS
≥10 years	5	3	7	9	
Complications					
Absent	7	2	10	8	NS
Present	15	12	9	12	
Severity†					
Child A	11	8	12	12	
Child B	7	5	4	7	NS
Child C	4	1	3	1	
History of hepatic encephalopathy††					
Absent	18	14	19	20	**
Present	4	0	0	0	
Hyperammonemia	20	10	16	13	§

NOTE. A diagnosis of SHE was made when the results of all three of the quantitative psychometric tests were abnormal. The inbalance in patients' numbers between group S-L and group S-NL was caused by three dropout patients in group S-NL who did not receive psychometric tests at week 4 and 8.

Abbreviations: NS, not significant; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus.

* $P < .05$ (group S-NL vs. group NS-NL). ** Impossible to analyze, because the number of cells with less than five of expected values was less than 50%.

† Child scale.

†† Overt encephalopathy (grade II or more advanced).

§ $P < .05$ (group S-L vs. group NS-NL).

ces, diabetes mellitus, and gallstones), hyperammonemia, or the history of overt hepatic encephalopathy. The mean age of the SHE group was significantly higher than that of the non-SHE group, but the age distributions of the patients less than 60 years and those 60 years or older were not significantly different between the two groups.

Lactulose was administered to 22 patients in the SHE group and to 19 in the non-SHE group. Thus, the patients were divided into four groups (SHE patients administered lactulose/not administered lactulose: group S-L/group S-NL; non-SHE patients administered lactulose/not administered lactulose: group NS-L/group NS-NL) (Table 2). No significant difference among the four groups was observed in the clinical characteristics of the patients (sex, severity of liver damage, history of overt encephalopathy, etc.). The mean age of group S-NL was significantly higher than that of group NS-NL, but the age distributions of the patients less than 60 years and those 60 years or older were not significantly different among the four groups. Although the mean number of the abnormal psychometric test results was significantly different between the SHE group (3.0 ± 0.0) and non-SHE group (1.2 ± 0.8), the mean number was not significantly different between groups S-L and S-NL or between groups NS-L and NS-NL, which should be compared with each other.

In the SHE patients administered lactulose (group S-L), the mean number of abnormal psychometric test results decreased significantly 4 and 8 weeks after the beginning of the administration as compared with the number before the administration ($P < .01$ for both) (Table 3). The mean number of abnormal psychometric test results at 8 weeks was smaller in the SHE patients administered lactulose (group S-L) than in the group not administered lactulose (group S-NL), although the difference was not significant ($P = .06$). In the non-SHE patients, in contrast, the mean number at the beginning of the study was smaller than that in the SHE patients, and no significant decrease was observed after lactulose administration for 4 or 8 weeks (group NS-L).

Serial changes in the prevalence of SHE after the beginning of lactulose administration were evaluated (Fig. 1). In the SHE patients administered lactulose (group S-L), the inci-

TABLE 3. Changes in Mean Number of Abnormal Psychometric Test Results in SHE and Non-SHE Patients Administered and Not Administered Lactulose

	After Lactulose Administration		
	0 wk	4 wk (mean score)	8 wk
SHE patients			
Lactulose (group S-L) (n = 22)	3.0 ± 0.0*	2.5 ± 0.8†	2.4 ± 0.7† (20)
No-lactulose (group S-NL) (n = 14)	3.0 ± 0.0*	2.8 ± 0.4	2.7 ± 0.9‡ (13)
Non-SHE patients			
Lactulose (group NS-L) (n = 19)	1.1 ± 0.9	1.3 ± 1.2	1.2 ± 1.0 (18)
No-lactulose (group NS-NL) (n = 20)	1.2 ± 0.7	1.2 ± 1.1	0.9 ± 1.0

NOTE. The values in parentheses are the numbers of patients examined. Four patients did not perform the psychometric tests at 8 weeks.

* A diagnosis of SHE was made when the results of all three of the quantitative psychometric tests were abnormal. Mean ± SD.

† $P < .01$ by the Wilcoxon test (0 weeks vs. 4 [8] weeks in group S-L).

‡ $P = .06$ (group S-L [8 weeks] vs. group S-NL [8 weeks]).

TABLE 4. Status of Lactulose Administration at the End of the Study and 6 Months After the Study

	Status of Lactulose Administration		
	At the End of the Study		Six Months After the Study
SHE patients*			
Lactulose (group S-L)	19	Continued	18
		Discontinued	1
No-lactulose (group S-NL)	13	Still not administered	8
		Started	5
Non-SHE patients			
Lactulose (group NS-L)	14	Continued	11
		Discontinued	3
No-lactulose (group NS-NL)	16	Still not administered	12
		Started	4

NOTE. The values are the number of patients.

* Lactulose administration was started during the follow-up period in 5 of the 13 SHE patients not administered lactulose during the study (group S-NL) (considered to be a significant change from nonadministered cases to administered cases). $P < .05$ by χ^2 test [6 months after the study: group S-L vs. group S-NL]).

dence of SHE was significantly less frequent 4 and 8 weeks after the beginning of the administration as compared with that before the administration ($P < .01$ for both). SHE was observed significantly less frequently in the lactulose-treated group (group S-L) than in the untreated group (group S-NL) at week 8 ($P < .05$). In the non-SHE group, three of the lactulose-treated patients and two of the untreated patients were temporarily diagnosed as having SHE at week 8.

The status of lactulose administration 6 months after the end of the study period was evaluated in 62 patients (Table 4). The administration was continued in many SHE patients (18 of 19 [95%]), and lactulose administration was started during the follow-up period in 5 (38%) of the 13 patients not administered lactulose during the study period, with 8 (62%) remaining untreated with lactulose. These results suggest that the change from nonadministered cases to administered cases was significant in the SHE patient group ($P < .05$) but not in the non-SHE patient group. In other words, SHE patients not administered lactulose during the test period had to start lactulose administration during the follow-up period.

Overt encephalopathy (≥ grade II) was observed during the follow-up period in only 1 SHE patient and 1 non-SHE patient of the 62 subjects evaluated. Symptoms considered to be side effects of lactulose were observed in 11 (26%) of the 43 patients in whom side effects were evaluated. They were: diarrhea in 8 (19%), soft stools in 1 (2%), anorexia in 1 (2%), abdominal pain in 1 (2%), vomiting in 1 (2%), and glycosuria in 1 (2%).

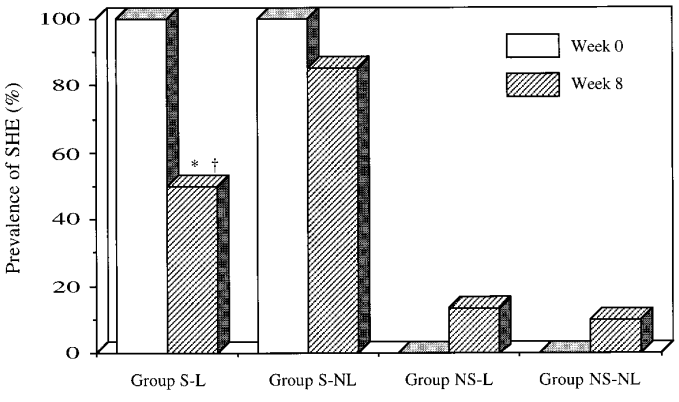

FIG. 1. Serial changes in the prevalence of SHE in the SHE and non-SHE patients administered and not administered lactulose during the test period. Only the data at week 0 and week 8 are shown. Number of subjects diagnosed with SHE according to the criteria shown in the text/number of subjects examined × 100 (%). The numbers of patients examined are described in Table 3. *$P < .01$ by the χ^2 test (0 weeks vs. 8 weeks in group S-L). †$P < .05$ (8 weeks in group S-L vs. 8 weeks in group S-NL).

DISCUSSION

There are a few recent studies of the efficacy of lactulose treatment in patients with SHE, e.g., an examination of the administration of lactulose or sucrose (90 mL/d) to 32 patients with SHE in a double-blind cross-over design.[13] However, poor drug compliance because of side effects such as abdominal discomfort has been suggested as a problem with lactulose therapy. In another study, lactulose (mean dose, 26 g adjusted to produce two bowel movements per day) and lactitol improved the motor ability on quantitative psychometric tests to a similar degree in 14 patients with SHE after a 2-month administration in a cross-over comparative design (randomization by the envelope method).[14] Additionally, neurological functions, electroencephalogram (EEG) findings, and QOL (sickness impact profile) were examined to evaluate whether lactulose improved the QOL in 40 patients with cirrhosis showing hyperammonemia (mostly Child A), in a double-blind trial of 6-month lactulose administration (30 g, which corresponds to 50 mL of 60% syrup).[15] However, no significant difference was observed in the parameters examined. A higher dose may have been necessary.

In Japan, the effects of lactulose on SHE have been studied only in a small number of subjects by Sato,[16] and he suggested the necessity of further evaluation of the relationship between the optimal dose of lactulose and the severity of cirrhosis.

In the present study, the efficacy of lactulose treatment was evaluated quantitatively by psychometric evaluation methods. Of the psychometric tests, the number connection test and the symbol digit test and block design test of the Wechsler adult intelligence scale (revised) are considered to be simple and reliable tests for the diagnosis of SHE.[11] Neuropsychological performance is known to be influenced by age, education, and repetitive testing.[17] In the present study, therefore, the psychometric tests were estimated with age-matched normal values. However, our previous study showed no influence of the education period (more than 90% of Japanese have attended school for at least 12 years) on psychological tests,[12] and thus the period of education was not considered. In addition, the patients' three performances of the tests at intervals of 4 weeks did not produce a significant difference in their results.

In the present study, the results of the three psychometric tests showed the prevalence of SHE to be 48% of the 75 patients, many of whom had well-compensated cirrhosis. This frequency is reasonable, because patients with cirrhosis who showed hyperammonemia at the time of the study or in the past were selected as the subjects.

When lactulose was administered to the patients with SHE at an ordinary dose for 8 weeks, significant improvements were observed in psychometric functions as compared with the level before the administration and with the untreated group. The results also suggest that lactulose reduced the blood ammonia concentration in both the SHE and non-SHE patients (data not shown).

The indications for the use of lactulose in Japan are considered to be as follows: alleviation of psychiatric and neurological symptoms, and EEG abnormalities and flapping tremor (asterixis), which are associated with hyperammonemia. However, the observations of the present study suggest that the indications for lactulose administration may not necessarily be restricted to the clinical state with overt hepatic encephalopathy (grade II or more advanced) and flapping tremor. Lactulose treatment should be begun with a low-protein diet if SHE is considered to be present on the basis of the results of a simple psychometric test such as the number connection test and the blood ammonia concentration. Abnormal EEG findings, which are included among the indications for the use of lactulose, were not evaluated in this study. However, based on the results of a previous study of EEG (topographic brain mapping) in patients with SHE,[18] many of the present subjects would have no abnormalities in conventional EEG recordings except for evoked potentials.

There have been a number of reports of improvements in the blood ammonia concentration in patients with hepatic encephalopathy by lactulose administration, but reports of improvements in the ammonia concentration in cirrhotic patients without overt encephalopathy have been scarce. In addition, the lactulose administration was continued after this study in many patients with SHE, and, at the follow-up examination 6 months after the study, the frequency of subjective symptoms such as malaise and sleep disturbance was reduced in the SHE patients receiving lactulose (data not shown). The neuropsychological defects found in SHE may have a negative effect on the patient's daily life.[19] Therefore, lactulose is expected to contribute to improvements in the QOL of cirrhotic patients with SHE, and the results of this study warrant further evaluation of the effects of lactulose administration on the QOL in a larger series of SHE subjects.

REFERENCES

1. Rikkers L, Jenko P, Rudman D, Freidas D. Subclinical hepatic encephalopathy detection, prevalence and relationship to nitrogen metabolism. Gastroenterology 1978;75:462-469.
2. Gitlin N. Subclinical portal-systemic encephalopathy. Am J Gastroenterol 1988;83:8-11.
3. Zeneroli ML, Cioni G, Uezzelli C, Grandi S, Crisi G, Luzietti R, Ventura E. Prevalence of brain atrophy in liver cirrhosis patients with chronic persistent encephalopathy. Evaluation by computed tomography. J Hepatol 1987;4:283-292.
4. O'Carroll RE, Hayes PC, Ebmeier KP, Dougall N, Murray C, Best JJ, Bouchier IR, et al. Regional cerebral blood flow and cognitive function in patients with chronic liver disease. Lancet 1991;37:1250-1253.
5. Watanabe A, Murakami J, Ando T, Hioki O, Wakabayashi H, Higuchi K. Reduction of increased signal intensity in the basal ganglia on T1-weighted MR images during treatment of hepatic encephalopathy. Int Med 1993;32:10-14.
6. Bircher J, Müller J, Guggenheim P, Haemmerli UP. Treatment of chronic portal systemic encephalopathy with lactulose. Lancet 1966;1:890-892.
7. Conn HO, Leevy CM, Vlahcevic ZR, Rodgers JB, Maddrey WC, Seeff L, Levy LL. Comparison of lactulose and neomycin in the treatment of chronic portal systemic encephalopathy. A double blind controlled trial. Gastroenterology 1977;72:573-583.
8. Takahashi Y, Shimizu M. Nation-wide investigation of fulminant hepatitis—definition and relationship between prognosis and days from the onset to the appearance of consciousness impairment. Proceed 12th Inuyama Symp., Chugai Igaku Co., Tokyo, Japan, 1982:116-125 [in Japanese].
9. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973;60:646-649.
10. Shiota T. Quantitative psychometric testing and subclinical hepatic encephalopathy—comparative study between encephalopathy and non-encephalopathic patients with liver cirrhosis. Acta Med Okayama 1984;38:193-205.
11. Higuchi K, Shimizu Y, Numbu S, Miyabayashi C, Takahara T, Saito S, Hioki O, et al. Effects of an infusion of branched chain amino acids on neurophysiological and psychometric testings in cirrhotic patients with mild hepatic encephalopathy. J Gastroenterol Hepatol 1994;9:366-372.
12. Watanabe A, Tsuchida T, Yata Y, Kuwabara Y. Evaluation of neuropsychological function in patients with liver cirrhosis with special reference to their driving ability. Metabol Brain Res 1995;10:239-248.
13. McClain CJ, Potter TJ, Kromhout JP, Zieve L. The effect of lactulose on psychomoter performance tests in alcoholic cirrhosis without overt hepatic encephalopathy. J Clin Gastroenterol 1984;6:325-329.
14. Morgan MY, Alonso M, Stanger LC. Lactitol and lactulose for the treatment of subclinical hepatic encephalopathy in cirrhotic patients. A randomized, cross-over study. J Hepatol 1989;8:208-217.
15. Quero JC, Groeneweg M, Meulstee J, Hop WCJ, Schalm SW. Does a low-dose of lactulose improve quality of life in patients with liver cirrhosis? In: Record H, ed. Advances in Hepatic Encephalopathy and Metabolism in Liver Disease. Boca Raton: CRC Press, 1997:459-465.
16. Sato S. Treatment of subclinical encephalopathy: lactulose. New Remedies and Therapy 1994;31:797-804 [in Japanese].
17. Quero JC, Hartmann IJC, Meulstee J, Hop WCJ, Schalm SW. The diagnosis of subclinical hepatic encephalopathy in patients with cirrhosis using neuropsychological tests and automated electroencephalogram analysis. HEPATOLOGY 1996;24:556-560.
18. Sagalés T, Gimeno V, de la Calzada MD, Casellas F, Dolors Maciá M, Villar Soriano M. Brain mapping analysis in patients with hepatic encephalopathy. Brain Topogr 1990;2:221-228.
19. Schomerus H, Hamster W, Blunck H, Reinhard U, Mayer K, Döll W. Latent portasystemic encephalopathy. I. Nature of cerebral functional defects and their effect on fitness to drive. Dig Dis Sci 1981;26:622-630.