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Lactitol Vs. Lactulose in the Treatment of Acute Hepatic Encephalopathy in Cirrhotic Patients: A Double-Blind, Randomized Trial

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Lactitol (β-galactosido-sorbitol) is a nonabsorbable disaccharide available as a powder which, in open comparison, is as effective as lactulose in the treatment of chronic hepatic encephalopathy, but is better tolerated. Twenty-five cirrhotic patients experiencing 28 episodes of acute hepatic encephalopathy were randomized blindly to treatment with either lactitol (n = 15) or lactulose (n = 13). The sugars were dispensed in solutions identical in appearance, taste and pH and of similar osmolarity, which contained either 66.7 gm per 100 ml lactitol or 66.7 ml (44.5 gm) per 100 ml lactulose syrup. The initial dose of 0.75 ml per kg was adjusted to produce two semisoft stools per day. Patients were assessed every 12 hr for 5 days. There were no significant differences in sex ratio, age, body weight, clinical status, duration and extent of coma, etiology of liver disease or of heptic encephalopathy between the two groups of patients on entry to the trial. An adequate catharsis was obtained with an equivalent mean (± 1 S.D.) daily dose of 26 ± 5 gm lactitol or 31 ± 7 ml (21 ± 5 gm) lactulose syrup. During the trial, significant improvements occurred in clinical status and psychometric performance and in the electroencephalogram mean cycle frequencies in the majority of patients in both groups. At the end of the trial, 67% of the patients in the lactitol group and 69% of the lactulose group were clinically normal. However, patients treated with lactitol responded significantly more quickly than patients treated with lactulose. Thus, at 24, 36, 48 and 72 hr, significantly greater mean percentage improvements were seen in PSE Indices in patients receiving lactitol than in patients receiving lactulose. Both sugars are effective in the treatment of acute hepatic encephalopathy in cirrhotic patients, but patients treated with lactitol respond significantly more quickly. Lactitol may be the treatment of choice for this condition.

Lactulose (β-galactosido-fructose) was first used to treat hepatic encephalopathy in 1966 (1). Since then, it has become the treatment of choice for both the acute and chronic forms of this syndrome (2). Lactulose is, however, generally prescribed as a syrup in which the parent compound is contaminated by other sugars, principally galactose and lactose. The excessive sweetness of the syrup is unacceptable to a number of patients, and its use may be associated with the development of nausea, flatulence and abdominal discomfort (2). Additionally, even after prolonged use, the cathartic effect of this sugar may be unpredictable (3).

Recently, the chemical, physiological and nutritional characteristics of lactitol (β-galactosido-sorbitol) have been described (4). This compound is a disaccharide analog of lactulose which is neither absorbed nor broken down in the small intestine (5), but is extensively metabolized by colonic bacteria (6). In theory, therefore, lactitol should be effective in the treatment of hepatic encephalopathy. However, as it can be produced in a chemically pure crystalline form, which can be dispensed as a powder, and as it is only fractionally as sweet as lactulose, it should produce fewer side effects. To date, lactitol has been used successfully to treat one patient with chronic hepatic encephalopathy intolerant of other medication (7) and five patients with chronic hepatic encephalopathy previously maintained on long-term lactulose (3). In the latter study, lactitol was found to be at least as efficacious as lactulose, but was preferred as a treatment by all five patients because its cathartic effect was more predictable, its presentation in powder form was more convenient and its less sweet taste preferred.

The aim of the present study was to assess the efficacy of lactitol vs. lactulose in double-blind comparison in the treatment of acute hepatic encephalopathy in patients with chronic liver disease.

PATIENTS AND METHODS

Twenty-seven patients, who between them experienced 30 episodes of acute hepatic encephalopathy, were admitted to the trial. All were known to have, or were suspected of having, chronic liver disease. Liver biopsy material obtained during earlier admissions to hospital was reviewed, and biopsies were performed in all patients previously undiagnosed. All patients showed clinical, psychometric and electroencephalographic evidence of hepatic encephalopathy of less than 4 days duration. Patients were excluded if they were infected with the hepatitis B virus, had an expectation of survival, based on

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clinical and biochemical observations of less than 5 days or had received treatment with neomycin or lactulose in the preceding 48 hr.

As soon as possible after admission to the hospital, patients underwent a detailed physical, neurological and psychometric assessment, with particular note being made of their mental status, the severity of asterixis and their performance on the Number Connection Test (NCT) (8). Electroencephalograms (EEGs) were performed by placing electrodes in accordance with the 10 to 20 system using both conventional montages and more widely spaced connections. A mean frequency figure was given for each record. Venous blood ammonia concentrations were measured using an enzymatic assay (9). Patients were then randomized by a sealed envelope system to treatment with lactulose or lactitol for 5 days.

Both sugars were dispensed as solutions of identical appearance and taste with similar osmolarity, optical density and pH, which contained either 0.67 gm lactitol powder per ml or 0.67 ml (0.45 gm) lactulose syrup per ml (Table 1). The trial solutions were given by mouth or if necessary via a nasogastric tube in an initial daily dose of 0.75 ml per kg body weight in four divided doses, which provided either 0.5 gm per kg lactitol or 0.5 ml (0.3 gm) per kg lactulose syrup. After the initial 24 hr, the volumes of the trial solution were adjusted every 12 hr, as needed, to obtain two soft or semisoft stools per day.

On entry into the trial and after the first 12 hr, the bowel was cleansed by use of phosphate enemata. Other drugs were prescribed as needed to treat the underlying liver disease or the events which precipitated the episode of encephalopathy. Dietary protein intake was restricted to 20 gm daily for the 5 days of the trial. However, once patients showed a sustained improvement in their mental status, dietary protein intake was increased in increments of 10 gm every third day.

Neurological observations were made hourly for 48 hr by the nursing staff. Detailed reassessments of neurological and psychometric status, the results of hematological and biochemical screening, and the EEG mean cycle frequencies were undertaken at 12, 24, 36, 48, 72, 96 and 120 hr by the medical staff. A stool chart was kept and a note taken of probable or definite side effects of treatment.

The severity of hepatic encephalopathy on entry to the trial and daily thereafter was estimated by calculating the portal-systemic encephalopathy (PSE) Sum and Index as described by Conn et al. (10). The PSE Sum is an arbitary index of the severity of hepatic encephalopathy derived by adding scores for the degree of abnormality in mental status, the severity of asterixis, the reduction of NCT time, the increase in blood ammonia concentration and the reduction in EEG mean cycle frequency, all expressed on a 0 to 4+ scale.

Mental state was assessed using the West Haven criteria for the grading of PSE (10).

Grade 0: No abnormality detected

Grade 1+: Trivial loss of awareness, euphoria or anxiety, shortened attention span, impairment of addition or subtraction

Grade 2+: Lethargy, disorientation for time, obvious personality change, inappropriate behavior

Grade 3+: Somnolence to semistupor, responsive to stimuli, confusion, gross disorientation, bizarre behavior

Grade 4+: Coma, tests of mental function not possible.

The number of seconds necessary to complete Part A of the NCT were graded as previously described (10).

Grade 0: <30 sec
Grade 1+: 31–50 sec
Grade 2+: 51–80 sec
Grade 3+: 81–120 sec
Grade 4+: >121 sec.

The presence or absence of asterixis was determined by extending the patients' arms and forearms, with the wrists dorsiflexed for at least 30 sec (10).

Grade 0: No flapping motions
Grade 1+: Rare flapping motions
Grade 2+: Occasional, irregular flaps
Grade 3+: Frequent flaps
Grade 4+: Almost continuous flapping motions.

If patients were unable to cooperate in the above manner, they were asked to squeeze two of the observers' fingers and the number of involuntary relaxations of grip quantified in the same manner. The EEG mean cycle frequencies were graded semiquantitatively (10).

Grade 0: Normal α rhythm > 9.0 cycles per sec (cps)
Grade 1+: 7–8.9 cps
Grade 2+: 5–6.9 cps
Grade 3+: 3–4.9 cps
Grade 4+: 2.9 cps or less.

Venous ammonia concentrations were assessed in a manner similar to that described previously (10).

Grade 0: <60 μmoles per liter
Grade 1+: 61–100 μmoles per liter
Grade 2+: 101–150 μmoles per liter
Grade 3+: 151–200 μmoles per liter
Grade 4+: >201 μmoles per liter.

TABLE 1. Formulation and physicochemical properties of the lactitol and lactulose solutions used to treat acute hepatic encephalopathy in cirrhotic patients in double-blind comparison

	Lactitol	Lactulose
Formulation	Lactitol—40 gm Distilled water—60 ml Blackcurrant syrup dropwise to color	Lactulose syrup—40 ml (66.7 gm/100 ml) Distilled water to 60 ml Blackcurrant syrup dropwise to color
Concentration (gm/100 ml)	66.7	44.5
Weight/ml (gm)	1.2053	1.2167
Refractive Index	1.422	1.422
Viscoscity (cps)	78.85	79.50
Osmolality (mOsm/liter)	2,947	2,911
pH	4.6	4.6
Optical rotation (°)	147.2	147.3

Each of these five components is arbitrarily weighted in proportion to its importance. Thus, mental state is weighted by a factor of three, while the other variables are assigned a factor of one. The PSE Sum is the total of the weighted scores; its maximum possible value is 28. If information on one or more of the components of the PSE Sum is not available, then PSE Sums calculated at different time points may not be directly comparable. The PSE Index was devised to take account of this eventuality. The PSE Index is the ratio of the estimated PSE Sum to the maximum possible PSE Sum. Comparison of PSE Indices permit changes in the severity of hepatic encephalopathy to be monitored at, for example, time points a and b, using the formula:

$$\%\ \text{change}_{a-b} = \frac{\text{PSE Index}_a - \text{PSE Index}_b}{\text{PSE Index}_a} \times 100.$$

If the PSE Index deteriorated between observation, a careful check was made on the stool frequency and the dose of the trial solution adjusted if necessary. Further investigations were instituted as indicated. If, at the next observation point, the PSE Index had deteriorated further, cleansing enemata were reinstituted twice daily. If improvement was not observed within 12 hr, neomycin (1 gm q.d.s.) was added to the treatment regimen. Patients failing to respond at this stage were regarded as treatment failures and were started on full doses of lactulose, neomycin and 12 hourly magnesium sulfate enemata. Patients who were for any reason unable to take oral medication were regarded as having discontinued treatment. They were managed with twice daily cleansing enemata, but monitoring was continued for the duration of the trial.

Differences in patient demography and in their clinical status on entry to the trial and on its completion were compared using an unpaired Student's t test. The efficacy of treatment was assessed by calculating the percentage change in PSE Index at Mann-Whitney U test was used to compare changes in PSE Index between the two treatment groups using an intention to treat analysis.

None of the individuals involved with patient management and monitoring during the trial had access to the trial codes.

This study was undertaken with permission from the Royal Free Hospital Ethics Committee. Written, informed consent was obtained from patients or their next of kin.

RESULTS

As a result of liver biopsy assessments, two patients were diagnosed as having acute fulminant hepatic failure and were excluded from the trial. There were no treatment failures, and it was not necessary to prescribe neomycin for any of the patients. Treatment was discontinued in three patients in the lactitol group. One patient developed nausea after 72 hr of treatment and could not tolerate oral medication; treatment was continued with cleansing enemata. This patient had, however, received lactitol during a previous admission for acute hepatic encephalopathy and on that occasion the drug had been well-tolerated and proved efficacious. Treatment in a further patient was stopped at 96 hr because of profuse gastrointestinal hemorrhage as a result of which she underwent esophageal transection which precluded oral medication for the remainder of the trial. The third patient was unable to take oral medication after the first 8 hr of the trial because he developed an ileus secondary to bowel infarction. These patients continued to be assessed and monitored, and their findings are included in the analysis. Thus, 28 episodes of hepatic encephalop-

TABLE 2. Details of cirrhotic patients studied and treated for acute hepatic encephalopathy with lactitol and lactulose

	Lactitol (n = 15)	Lactulose (n = 13)
Mean (±1 S.D.) age (yr)	48.4 ± 12.5 (range = 32–77)	48.3 ± 15.8 (range = 23–74)
Sex ratio	7 M:8 F	8 M: 5 F
Etiology of liver disease (n)		
Alcohol	8 (53.3%)	7 (54.6%)
Chronic active hepatitis	2 (13.3%)	3 (23.1%)
Others	5 (33.4%)	3 (23.1%)
Mean Pugh's Score[a]	10.8 ± 1.9	10.2 ± 2.9
(Range)	(7.0–13.0)	(7.0–15.0)
(Normal = 0–15)		
Child's Grade[b] B (n)	4	6
Child's Grade C (n)	11	7
Mean weight (kg)	64 ± 13	68 ± 15
Mean PSE Sum on entry (0–28)	13.3 ± 3.9	12.2 ± 5.2
Mean PSE Index on entry (0–1)	0.48 ± 0.14	0.46 ± 0.19
Mean duration of precoma before study (hr)	36.5 ± 25.9	28.3 ± 9.6
Precipitant of hepatic encephalopathy (n)		
Gastrointestinal bleeding	6 (40.0%)	8 (61.5%)
Infection	11 (73.3%)	8 (61.5%)
Hypokalemia	6 (40.4%)	5 (38.5%)
Multiple	11 (73.3%)	8 (61.5%)
Drugs within 48 hr of entry (n)		
Diazemuls	7 (53.8%)	6 (46.1%)
General anesthesia	2 (13.3%)	1 (7.7%)
Antibiotics	11 (73.3%)	10 (76.9%)
Potassium	8 (53.3%)	6 (40.0%)

[a] See Ref. (11).
[b] See Ref. (12).

athy occurring in 25 patients, 15 treated with lactitol and 13 treated with lactulose, were assessed. One patient received lactitol on two occasions, one received lactulose on two occasions and one patient was treated, on separate occasions, with both drugs.

The patients in the two treatment groups were similar in age, sex ratio, precipitant and severity of hepatic encephalopathy and in the severity of their liver disease (Table 2). On entry into the trial, the mean values for clinical assessment, EEG mean cycle frequency, NCT time, venous blood ammonia values and the PSE Sums and Indices were similar (Tables 3 and 4).

Significant improvements occurred in clinical status, psychometric performance, EEG mean cycle frequency and PSE Sums and Indices in the majority of patients in both groups during the trial (Tables 3 and 4). A mean (±1 S.D.) improvement in PSE Index of 53.8 ± 43.4% was observed in the lactitol group and in 51.7 ± 23.0% in the lactulose group by Day 5, by which time 10 patients (67%) treated with lactitol and 9 patients (69%) treated with lactulose were clinically normal. However, improvement occurred more quickly in patients treated with lactitol (Figure 1, a and b). Thus, after 24, 36, 48 and 72 hr of treatment, significantly greater mean percentage improvements were observed in PSE Indices in patients treated with lactitol than in patients treated with lactulose (Table 5).

There were no deaths during the trial. The three individuals in whom treatment with lactitol was discontinued died 6, 9 and 13 days after the trial, the first of bowel infarction and septicemia and the other two of uncontrollable gastrointestinal bleeding. One further patient treated with lactitol also died 13 days after the trial after developing hepatorenal syndrome. One patient treated with lactulose died 8 days after the trial as a result of uncontrollable gastrointestinal hemorrhage and sepsis. All five patients had severe liver disease.

Patients required a mean of 39 ± 7 ml (range = 24 to 48) lactitol solution or 46 ± 11 ml (range = 28 to 64) lactulose solution to achieve two semisoft stools per day. This is equivalent to a dose of 26 ± 5 gm (range = 16 to 32) lactitol or 31 ± 7 ml (range = 19 to 43) lactulose syrup or 21 ± 5 gm (range = 13 to 29) lactulose. The initial dose of 0.75 ml per kg was increased in two patients in each group because the response to treatment was inadequate. The initial dosage was reduced in six patients treated with lactitol and four patients treated with lactulose because of diarrhea, which was defined as the passage of four or more stools per day. In general, the diarrhea abated when the volume of solution was reduced, except in one patient treated with lactulose in whom diarrhea persisted to the end of the trial. In one other patient treated with lactulose, diarrhea was associated with the development of hypernatremia at 96 hr. He responded to rehydration and a reduction in the volume of trial solution given.

TABLE 3. Changes in weighted scores of the components of the PSE Sum, the PSE Sum and Index and the improvement in PSE Index in 15 cirrhotic patients with acute hepatic encephalopathy during treatment with lactitol

Assessment time (hr)	Mental state (0–4 + × 3)	Asterixis (0–4+)	EEG (0–4+)	NCT (0–4+)	Blood ammonia (0–4+)	PSE Sum (0–28)	PSE Index (0–1)	Improvement in PSE index (%)
0	5.2 ± 2.0	2.4 ± 1.0	2.0 ± 0.7	2.9 ± 1.3	0.8 ± 0.9	13.3 ± 3.9	0.48 ± 0.14	—
12	3.6 ± 3.3	2.1 ± 1.0	1.7 ± 0.6	2.7 ± 1.2	1.0 ± 0.8	11.1 ± 5.1	0.40 ± 0.18	15.2 ± 39.9
24	2.6 ± 2.7**	1.7 ± 0.9*	1.6 ± 0.7	2.1 ± 1.2*	0.9 ± 0.8	8.9 ± 4.6**	0.32 ± 0.16**	30.4 ± 44.9
36	1.5 ± 2.4****	1.3 ± 0.6***	1.7 ± 0.9	2.1 ± 1.3	0.6 ± 0.8	7.3 ± 4.8***	0.26 ± 0.17***	40.8 ± 52.2
48	1.7 ± 3.2****	1.3 ± 0.9***	1.7 ± 0.8	1.8 ± 1.1*	0.6 ± 0.6	7.1 ± 5.4***	0.25 ± 0.19***	40.7 ± 58.3
72	1.1 ± 2.9****	1.2 ± 0.8***	1.6 ± 0.9	1.7 ± 1.1*	0.7 ± 0.6	6.4 ± 5.2***	0.23 ± 0.19***	45.6 ± 55.1
96	1.0 ± 2.4****	1.0 ± 0.7****	1.4 ± 0.9	1.7 ± 1.0**	1.3 ± 0.9	6.3 ± 4.3***	0.23 ± 0.15***	45.7 ± 46.3
120	0.6 ± 1.6****	1.1 ± 0.6****	1.3 ± 0.9*	1.4 ± 1.0***	0.9 ± 0.9	5.3 ± 4.0****	0.19 ± 0.14****	53.8 ± 43.4

Values are expressed as mean ± 1 S.D. Significance of difference between values of measured variables during treatment and baseline values: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.005$; **** $p < 0.001$.

TABLE 4. Changes in weighted scores of the components of the PSE Sum, the PSE Sum and Index and the improvement in PSE Index in 13 cirrhotic patients with acute hepatic encephalopathy during treatment with lactulose

Assessment time (hr)	Mental state (0–4+ × 3)	Asterixis (0–4+)	EEG (0–4+)	NCT (0–4+)	Blood ammonia (0–4+)	PSE Sum (0–28)	PSE Index (0–1)	Improvement in PSE Index (%)
0	4.2 ± 2.8	2.2 ± 1.2	1.9 ± 0.7	2.9 ± 1.1	0.9 ± 0.7	12.2 ± 5.2	0.46 ± 0.19	—
12	3.9 ± 3.4	1.9 ± 0.9*	1.8 ± 0.7	2.9 ± 1.1	0.9 ± 0.8	11.2 ± 6.0	0.40 ± 0.21	10.0 ± 17.9
24	3.9 ± 3.6	1.9 ± 1.1	1.9 ± 0.7	2.6 ± 1.3	0.9 ± 0.8	11.2 ± 6.5	0.40 ± 0.23	12.3 ± 26.7
36	3.0 ± 3.3	1.8 ± 1.2*	1.7 ± 0.7	2.5 ± 1.2	0.6 ± 0.7	9.5 ± 6.3*	0.34 ± 0.23*	23.1 ± 32.9
48	2.8 ± 3.0*	1.5 ± 1.1*	1.6 ± 0.7	2.5 ± 1.2	0.8 ± 0.4	9.2 ± 5.6**	0.33 ± 0.20**	27.7 ± 25.7
72	1.8 ± 1.9***	1.5 ± 0.8***	1.5 ± 0.5**	2.2 ± 1.0*	1.1 ± 0.7	8.1 ± 4.1****	0.29 ± 0.15****	34.1 ± 15.0
96	0.9 ± 1.4****	1.2 ± 0.6****	1.5 ± 0.6*	1.8 ± 0.8***	0.7 ± 0.6	6.1 ± 2.6****	0.22 ± 0.09****	46.2 ± 17.4
120	0.7 ± 1.3****	1.0 ± 0.0****	1.2 ± 0.9**	1.6 ± 0.9****	0.7 ± 0.6	5.2 ± 2.6****	0.19 ± 0.09****	51.7 ± 23.0

Values are expressed as mean ± 1 S.D. Significance of difference between values of measured variables during treatment and baseline values: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.005$; **** $p < 0.001$.

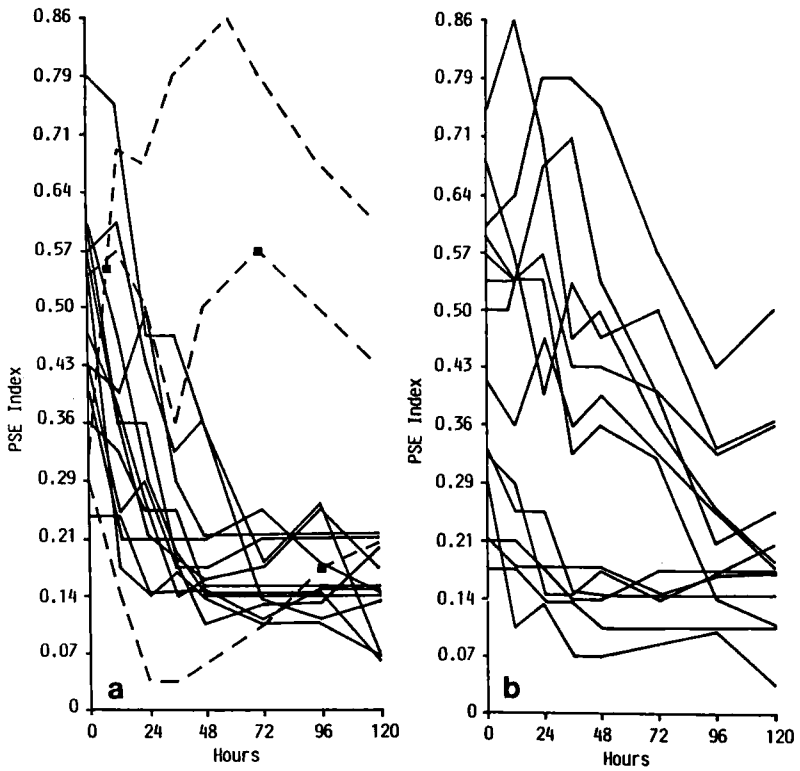

FIG. 1. (a) Changes occurring in PSE Index (10) in 15 patients with cirrhosis and acute hepatic encephalopathy during 5 days treatment with lactitol; - - - - = patients withdrawn from treatment but still monitored for entire trial period; ■ = time point of withdrawal from treatment. (b) Changes occurring in PSE Index (10) in 13 patients with cirrhosis and acute hepatic encephalopathy during 5 days treatment with lactulose.

TABLE 5. Summary of changes in encephalopathy occurring throughout the double-blind, randomized controlled trial of lactitol vs. lactulose in acute hepatic encephalopathy

	Lactitol (n = 15)		Lactulose (n = 13)	
	Entry	End	Entry	End
Mean clinical assessment (0–4)	1.7 ± 0.7	0.2 ± 0.5	1.4 ± 0.9	0.2 ± 0.4
	* $p < 0.005$		$p < 0.005$	
Mean EEG (>9.0 cps)	5.7 ± 1.3	7.0 ± 1.5	5.8 ± 1.3	7.6 ± 1.6
	$p < 0.05$		$p < 0.01$	
Mean NCT (<30 s)	104 ± 53	52 ± 23	97 ± 34	58 ± 23
	$p < 0.005$		$p < 0.001$	
Mean blood ammonia (<60 μmoles/liter)	65.8 ± 38.4	82.2 ± 35.5	79.5 ± 31.4	67.8 ± 29.1
	NS		NS	
Mean PSE Sum (0–28)	13.3 ± 3.9	5.3 ± 4.0	12.2 ± 5.2	5.2 ± 2.6
	$p < 0.001$		$p < 0.001$	
Mean PSE Index (0–1)	0.48 ± 0.14	0.19 ± 0.14	0.46 ± 0.19	0.19 ± 0.09
	$p < 0.001$		$p < 0.001$	
Mean % improvement in PSE Index by:				
12 hr	15.2 ± 39.9		10.0 ± 17.9	NS
24 hr	30.4 ± 44.9		12.3 ± 26.7	** $p < 0.05$
36 hr	40.8 ± 52.2		23.1 ± 32.9	$p < 0.05$
48 hr	40.7 ± 58.3		27.7 ± 25.7	$p < 0.02$
72 hr	45.6 ± 55.1		34.1 ± 15.0	$p < 0.01$
96 hr	45.7 ± 46.3		46.2 ± 17.4	NS
120 hr	53.8 ± 43.4		51.7 ± 23.0	NS

Values are expressed as mean ± 1 S.D. NS = not statistically significant. * Significance of difference between values at beginning and end of trial in each treatment group. ** Significance of differences between values during treatment with lactitol and lactulose.

DISCUSSION

Hepatic encephalopathy is the term used to describe the neuropsychiatric abnormalities which may arise in patients with liver disease (13–16). The syndrome is characterized clinically by disturbances of consciousness, personality and intellectual capacity as well as altered neuromuscular activity. In its most commonly observed form, hepatic encephalopathy manifests as a single or repeated episodes of cerebral impairment arising in patients with chronic liver disease often related to a specific precipitating event such as gastrointestinal bleeding, infection, diuretic overuse, constipation or dietary protein excess (17, 18). In approximately 50% of instances, however, no specific precipitating event is identified (19).

The pathogenesis of the syndrome remains speculative, but as it is potentially a fully reversible condition and is usually unaccompanied by any fixed structural changes in the brain, it can be regarded as a metabolic or neurophysiological disorder. Gut-derived toxins of nitrogenous origin are thought to play a role in the genesis of the syndrome; thus, treatment is aimed, somewhat empirically, at reducing the production and absorption of these compounds. Lactulose, which is a nonabsorbable disaccharide, is used extensively to treat hepatic encephalopathy, although its exact mechanism of action is unknown. It may, however, exert its beneficial effects by: (i) lowering colonic pH, thereby suppressing the absorption of unionized ammonia (20, 21); (ii) suppressing bacterial and intestinal ammonia generation (22, 23); (iii) stimulating the incorporation of ammonia into bacterial protein (24); (iv) decreasing intestinal transit time because of its cathartic properties (25) and hence reducing the time available for both the production and absorption of toxins, and (v) increasing fecal nitrogen excretion (26).

In general, lactulose is an extremely safe compound, although rarely it may produce profound diarrhea, resulting in dehydration and hypernatremia (27, 28). However, it is usually prescribed as a very sweet syrup for which many patients express an aversion and, as it is contaminated with other sugars, it tends to produce nausea, flatulence and abdominal discomfort (2). Additionally, even after prolonged usage, its cathartic effect is unpredictable (3).

Lactitol is a disaccharide which, like lactulose, is not absorbed in the small intestine (5), but is extensively metabolized by colonic bacteria (6). Unlike lactulose, however, it is available as a pure crystalline powder with a low relative sweetness. In open comparison, lactitol has been shown to be as effective as lactulose in the treatment of chronic, stable hepatic encephalopathy (3), but was preferred because of its less sweet taste, its more convenient formulation and the greater predictability of its cathartic effect.

The present double-blind, randomized trial was designed to evaluate the efficacy of lactitol in comparison with lactulose in the treatment of acute hepatic encephalopathy in patients with cirrhosis using comparable formulations for the sugars. All 25 patients studied had chronic liver disease and had acute hepatic encephalopathy of recent onset. In the majority of patients, a specific precipitating factor was identified, although it is interesting to note that in almost two-thirds of the patients, more than one such factor was present. Our patient population was selected only in that we attempted to exclude patients who would not survive the acute event and the small number of patients admitted with hepatitis B viral infection. The essentially unselected nature of our population is reflected in the complications which required discontinuation of treatment in three of the patients and the overall hospital mortality of 20%.

The patients in each treatment group were similar in age, sex ratio, cause of hepatic encephalopathy and severity of liver disease as assessed by Pugh's criteria and Child's modification of Pugh's scoring (11, 12). However 30.8% of patients treated with lactitol died during the hospital admission compared with only 8.3% in the lactulose group, suggesting that the patients in the lactitol group were perhaps more severely ill.

Similar overall improvements in neuropsychiatric status were observed in both treatment groups by the end of the 5-day trial. However, resolution of the signs and symptoms of hepatic encephalopathy was significantly more rapid in the lactitol-treated group. Patients who are irritable or confused are more difficult to care for and require greater medical supervision; patients in the deeper stages of coma are more likely to develop severe complications, such as aspiration pneumonia. A treatment regimen which produces a more rapid response is likely to be of greater benefit to the patients.

The fact that the patients treated with lactitol responded more rapidly suggests that the two sugars may act in a different manner, although this would not be expected on theoretical grounds. Recent evidence suggests that, although both sugars are metabolized by colonic bacteria, differences exist in the speed with which they are metabolized and in the degree of subsequent gas formation (Luginbuhl, M., personal communication). In addition, studies in healthy volunteers, from whom samples of cecal contents were obtained using a capsule technique, have shown that cecal bacterial counts of aerobic organisms and of enterococci are lower during ingestion of lactitol than during ingestion of lactulose (Lang, O. et al., Internal Zyma Report 1986, Study LACT-10-8416). These findings suggest that differences exist in the way in which these two sugars are metabolized in the colon, and this may explain the difference in their speed of action.

Lactitol and lactulose are both effective treatments for acute hepatic encephalopathy in patients with chronic liver disease. However, resolution of neuropsychiatric symptoms is more rapid with lactitol, suggesting that this sugar might be the treatment of choice for this condition.

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