*Clinical trials***Lactitol in the treatment of chronic hepatic encephalopathy: an open comparison with lactulose**

PHILIPPE L LANTHIER AND MARSHA Y MORGAN

From the Academic Department of Medicine, The Royal Free Hospital School of Medicine, London

SUMMARY Lactulose is currently the drug of choice for the treatment of hepatic encephalopathy. It is, however, only available as a syrup which is contaminated with other sugars. Consequently patients may express aversion to its excessively sweet taste and many experience nausea because of its hyperosmolarity. Lactitol is a disaccharide analogue of lactulose which can be produced as a pure crystalline powder with a low relative sweetness. Theoretically it should have the same therapeutic effects as lactulose but fewer side effects. Five patients with chronic hepatic encephalopathy on maintenance lactulose were monitored clinically, psychometrically, and by measurement of venous blood ammonia, electroencephalogram mean cycle frequency, and cerebral blood flow during three months treatment with lactulose and a similar period on lactitol. Lactitol was at least as efficacious as lactulose but was more acceptable because its cathartic effect was more predictable, its formulation was more convenient and its less sweet taste preferred. Lactitol is the ideal successor to lactulose for treatment of this condition.

Lactulose (β -galactosido-fructose) has been used since 1966 to treat hepatic encephalopathy¹ and is now accepted as the drug of choice for this condition.² This compound is, however, only available as a syrup in which the parent compound is contaminated by other sugars, principally galactose and fructose. Its excessively sweet taste is unacceptable to a number of patients and many experience nausea because of its hyperosmolarity. Despite these disadvantages no analogues with more favourable physicochemical properties have been developed for use in this condition.

Recently lactitol (β -galactosido-sorbitol), a disaccharide analogue of lactulose has been described.³ This compound is easily produced from lactose in a chemically pure form and can be dispensed as a powder which has a relative sweetness, depending on its concentration, of only 35% compared with sucrose. Otherwise it is similar to lactulose in that it is neither broken down nor absorbed in the small intestine, but is extensively metabolised by colonic bacteria. It would seem the ideal successor to lactulose for treatment of hepatic

encephalopathy and has been used successfully to treat one patient with this condition.⁴

In the present study five patients with chronic hepatic encephalopathy, previously on long term maintenance therapy with lactulose, were treated with lactitol for three months under carefully monitored conditions. As close monitoring is known to have a beneficial effect on this condition, possibly because of better compliance with therapy, a monitored three month treatment period on lactulose was included for comparison.

Methods**PATIENTS**

The study group comprised five patients with cirrhosis and chronic hepatic encephalopathy maintained in stable condition by use of protein restriction and oral lactulose (Table 1). All five patients experienced worsening of their clinical condition, psychometric performance, and electroencephalogram mean cycle frequency if inadvertently allowed to become constipated or to discontinue protein restriction or lactulose. None of the alcoholic patients had abused alcohol for at least two years. All patients were admitted to hospital for

Address for correspondence: Dr M Y Morgan, Medical Unit, Royal Free Hospital, Pond Street, Hampstead, London NW3 2QG.

Received for publication 8 June 1984

Table 1 Details of five patients on maintenance lactulose for treatment of chronic hepatic encephalopathy

Patient	Age (yr)	Sex	Aetiology of cirrhosis	Serum bilirubin ($\mu\text{mol/l}$) (5–17)*	Serum AST† (U/l) (5–40)	Plasma albumin (g/l) (35–50)	Pro-thrombin (s) (control = 13)	Portal systemic shunt
RG	63	M	Alcoholic	29	78	32	17	Spontaneous
JB	61	M	Alcoholic	20	37	33	17	Spontaneous
LC	53	M	Alcoholic	5	46	34	13	Spontaneous
EH	54	M	Cryptogenic	38	27	38	21	Meso-caval shunt 1975
NT	41	M	Cryptogenic	57	41	32	15	Porto-caval shunt 1967

Duration of encephalopathy (mo)		Duration of treatment (mo)			
EEG	Clinical	Protein restriction	Lactulose	Bromocriptine	Present treatment (daily)
16	4	4	4	—	40 g protein 20 ml lactulose
5	5	5	5	—	40 g protein 20 ml lactulose
22	22	22	22	14	30 g protein 40 ml lactulose 7.5 mg bromocriptine
90	90	36	90	—	60 g protein 30 ml lactulose
132	132	132	132	60	30 g protein 20 ml lactulose 10 mg bromocriptine

* Reference range in parentheses. † AST = Aspartate aminotransferase.

an assessment on maintenance lactulose. A detailed clinical examination was undertaken and psychometric performance evaluated using the Reitan trial test,⁵ the digit copying subtest of the Kendrick battery⁶ and the digit symbol and digit span subtests of the Weschler Adult Intelligence Scale (WAIS).⁷ Routine haematological and biochemical investigations were undertaken using standard laboratory procedures and the venous blood ammonia was measured daily for three days.⁸ Electroencephalograms (EEGs) were performed daily for three days and a mean frequency figure given for each record. Cerebral blood flow was estimated by the inhalation of radioactive xenon (^{133}Xe).⁹

Patients were discharged from hospital with their dietary regime and drug treatment unchanged. They were instructed to alter the dose of lactulose as necessary to ensure passage of two semi-soft stools per day. At monthly intervals patients were seen in the outpatient department for reassessment of their clinical status and measurement of their Reitan trial test, venous blood ammonia concentration and EEG mean cycle frequency. After three months of careful monitoring on lactulose patients were readmitted to hospital for a further full assessment.

After reassessment lactitol was substituted for

lactulose in the treatment regime in a dose of 0.5 g/kg daily to be increased to 0.75 g/kg if necessary to ensure passage of two semi-soft stools per day. Patients were assessed monthly in the outpatient department as before and then readmitted to hospital after three months treatment with lactitol for a final reassessment.

Throughout the trial patients kept a diary in which they recorded their daily drug dosage, stool frequency and consistency, and an assessment of symptoms and side effects if any. Each month they were asked to score treatment efficacy and acceptability on a scale of 1 = poor to 4 = excellent.

The treatment protocol was approved by the Royal Free Hospital Ethics Committee and informed consent was obtained from all patients studied.

Results

CLINICAL RESPONSE

When assessed on maintenance lactulose three patients (JB, LC, EH) showed no clinical evidence of hepatic encephalopathy while the remaining two patients (RG, NT) complained of drowsiness in the late afternoons and mild slurring of speech. After

three months close monitoring on lactulose, patient RG became clinically normal while the remaining four patients were clinically unchanged. During subsequent treatment with lactitol patients RG, JB, LC, and EG remained clinically normal though patient NT continued to show evidence of mild hepatic encephalopathy.

PSYCHOMETRIC TESTING (Table 2)

All five patients showed substantial deficits on psychometric testing when evaluated on maintenance lactulose. No changes were observed in mean test scores after monitored treatment over three months with either lactulose or lactitol. Although individual patients showed improvement in one or more tests in both treatment periods their performance overall did not change substantially.

VENOUS BLOOD AMMONIA (Fig. 1)

The mean ($\pm$ ISD) venous blood ammonia concentration on maintenance lactulose was 90 ± 38 $\mu\text{mol/l}$ (reference range 15–60 $\mu\text{mol/l}$); values were raised in patients JB, LC, and NT. Mean venous blood ammonia concentrations remained raised after monitored treatment over three months with both lactulose, 88 ± 23 $\mu\text{mol/l}$ and lactitol, 75 ± 15 $\mu\text{mol/l}$.

ELECTROENCEPHALOGRAPHY (Fig. 2)

When assessed on maintenance lactulose all five

Fig. 1 Changes in venous blood ammonia in five patients with chronic hepatic encephalopathy while on maintenance lactulose, after three months of monitoring on lactulose and three months monitoring on lactitol. Each value is the mean of three measurements made at daily intervals. Reference range 15 to 60 $\mu\text{mol/l}$.

Table 2 Results of psychometric tests in five patients with chronic hepatic encephalopathy on maintenance lactulose, after three months monitoring on lactulose and after three months monitoring on lactitol

Patient	Reitan A trial (s) (normal 30)			Digit copying (maximum 208)		
	Maintenance lactulose	Monitored lactulose	Monitored lactitol	Maintenance lactulose	Monitored lactulose	Monitored lactitol
RG	79	81	71	96	108	117
JB	50	37	40	133	138	143
LC	29	25	22	136	138	117
EH	37	29	32	192	177	182
NT	69	71	78	60	60	57
Mean	53	49	49	124	124	123
SD	21	26	25	43	43	46
Patient	Digit symbol (maximum 90)			Digit span (maximum 17)		
	Maintenance lactulose	Monitored lactulose	Monitored lactitol	Maintenance lactulose	Monitored lactulose	Monitored lactitol
RG	23	29	34	9	10	10
JB	55	47	55	16	16	16
LC	38	32	33	8	8	8
EH	54	53	54	12	12	14
NT	0	0	21	0	0	0
Mean	34	32	39	9	9	10
SD	23	21	15	6	6	6

Fig. 2 Changes in electroencephalogram (EEG) mean cycle frequency in five patients with chronic hepatic encephalopathy while on maintenance lactulose, after three months of monitoring on lactulose and three months monitoring on lactitol. Each value is the mean of three measurements of mean cycle frequency at daily intervals. Mean cycle frequency in an alert adult >8.9 cps.

Fig. 3 Changes in cerebral blood flow in five patients with chronic hepatic encephalopathy while on maintenance lactulose, after three months of monitoring on lactulose and three months monitoring on lactitol. Reference range 45 ± 5 ml/100 g brain/min.

patients showed mild to moderate abnormalities of their EEG with alpha wave slowing to a mean frequency of 7.3 ± 1.2 cps (normal alert adult >8.9 cps). Mean EEG frequencies remained reduced after monitored treatment over three months with both lactulose, 7.5 ± 0.5 cps and lactitol, 8.0 ± 0.6 cps. Patient NT, however, showed an improvement in EEG frequency when monitored on lactulose which was sustained during treatment with lactitol, while patients RG and LC showed little change in EEG frequency on monitored lactulose but improvement following lactitol.

CEREBRAL BLOOD FLOW (Fig. 3)

When assessed on maintenance lactulose all five patients showed reduction in cerebral blood flow to a mean of 33.0 ± 4.9 ml/100 g brain/min (reference range 45 ± 5 ml/100 g brain/min). After monitored treatment with lactulose for three months the mean cerebral blood flow remained unchanged, 32.5 ± 3.9 ml/100 g brain/min, and little if any change was observed in individual measurements. After treatment with lactitol the mean cerebral blood flow remained low, 37.7 ± 4.6 ml/100 g brain/min although a substantial increase in flow was observed in patients EH and NT.

PATIENTS ASSESSMENT (Table 3)

Three patients, RG, JB, and EH considered lactitol to be as efficacious as lactulose, while patients LC and NT considered its effect superior. All five

patients felt that treatment with lactitol was more acceptable. Stated reasons for the greater acceptability of lactitol included: (1) The cathartic effect of lactitol was more predictable. In order to achieve two semi-soft stools per day patients required a mean of 44 ml (range 20 to 100 ml) of lactulose or 64 g (48 to 84 g) of lactitol. All five patients found that stool frequency was more predictable with lactitol (Fig. 4). (2) The formulation of lactitol was more convenient. Four patients were in full time employment and found lactitol more convenient to use during working hours; most added it to beverages or food as a sweetener. Patients LC, EH, and NT had avoided holidays while on maintenance lactulose because of difficulties experienced in transporting the

Table 3 Patients assessment of the efficacy and acceptability of treatment with lactulose and lactitol for chronic hepatic encephalopathy

Patient	Lactulose		Lactitol	
	Efficacy (1-4)	Acceptability (1-4)	Efficacy (1-4)	Acceptability (1-4)
RG	2	2	2	4
JB	2	2	2	4
LC	1	2	3	4
EH	2	2	2	4
NT	2	2	3	4

Fig. 4 Daily stool frequency in patient EH during the second month of monitored treatment with either lactulose or lactitol for chronic hepatic encephalopathy. Throughout the patient took a 60 g protein diet and no other medication.

quantities of drug required and because of the uncertainty of its effects. All three patients holidayed without incident on lactitol. (3) The less sweet taste of lactitol was preferred by all five patients.

SIDE EFFECTS

Patients JB and EH experienced abdominal discomfort, flatulence and some urgency of defaecation whilst on lactulose but were symptom free on lactitol.

No other side effects were noted. No changes occurred in routine haematological or biochemical values on either treatment.

Discussion

Chronic hepatic encephalopathy is the term used to describe the neuropsychiatric syndrome which may complicate chronic liver disease.¹⁰ The syndrome is characterised clinically by disturbances of consciousness, personality, and intellectual capacity as well as increased neuromuscular activity. Psychometric performance is often grossly disturbed and provides a better and more sensitive measure of the neuropsychiatric deficit than clinical examination.¹¹ The EEG mean cycle frequency may be slowed, cerebral blood flow reduced and venous blood ammonia concentration raised. Although these variables correlate poorly with the clinical state and with each other, repeated measures are useful in assessing progress. Many of the abnormalities observed reverse when the condition is successfully treated.

The patients in the present study were on maintenance therapy for chronic hepatic

encephalopathy and exhibited few, if any, clinical abnormalities. All five patients, however, showed considerable neuropsychiatric deficits on psychometric testing, abnormal EEG patterns, reduced cerebral blood flow and high normal or frankly raised venous blood ammonia concentrations. These findings well illustrate the relative insensitivity of the clinical examination and the need to use several variables in the assessment of this condition.

The pathogenesis of this syndrome remains speculative. There is general agreement, however, that in the majority of instances hepatic encephalopathy is a metabolic/neurophysiological disorder of the brain and that gut produced toxins play a role in its genesis.¹² Treatment of the condition is therefore aimed, somewhat empirically, at reducing the production and absorption of these toxins and is achieved by decreasing the gut protein load, altering the intestinal flora, reducing the rate and absorption of protein and protein fragments, decreasing intestinal transit time and bowel cleansing.

The value of lactulose in the treatment of hepatic encephalopathy has been amply shown.² This synthetic disaccharide is not absorbed but is hydrolysed by colonic bacteria principally to lactic and acetic acids. Its precise mode of action is uncertain but it might exert its beneficial effects by lowering colonic pH thereby reducing the absorption of un-ionised ammonia, by encouraging the incorporation of ammonia into bacterial protein, by decreasing intestinal transit time because of its cathartic effect or by an anti-endotoxin effect.¹³

In general lactulose is an extremely safe drug although rarely it may produce profound diarrhoea and result in dehydration and hypernatraemia.¹⁴ Lactulose is, however, only available as a very sweet syrup for which many patients express an aversion and as it is contaminated with other sugars it is hyperosmolar and may thus produce nausea, flatulence, and abdominal discomfort. Additionally even after prolonged usage its cathartic effects are not entirely predictable; therefore compliance with treatment may be poor.

Lactitol is a disaccharide analogue of lactulose which like the earlier compound is not absorbed in the small intestine but is extensively metabolised by colonic bacteria.³ Unlike lactulose, however, it is easily produced in a chemically pure form and can be dispensed as a powder which has a low relative sweetness.³ In theory it should be as effective as lactulose in the treatment of hepatic encephalopathy and its properties might confer additional benefits.

In the present study lactitol was given to five patients with chronic hepatic encephalopathy who had been maintained on long term lactulose.

Lactitol was at least as efficacious as lactulose in the treatment of this condition. All five patients, however, found treatment with lactitol more acceptable because its cathartic effect was more predictable, its formulation was more convenient and its less sweet taste was preferred. Lactitol would appear to be the ideal successor to lactulose for the treatment of hepatic encephalopathy. Further studies with this compound are justified.

We thank Professor Dame Sheila Sherlock for allowing us to study patients under her care, Dr Jean Kennedy and her staff for performing the electroencephalograms and Dr Ian James and his staff for the cerebral blood flow estimations. PLL was supported by the Medical Council on Alcoholism. MYM is William Gibson Scholar of the Royal Society of Medicine, London. Lactitol was kindly supplied by Dr G-P Ravelli of Zyma SA, Nyon, Switzerland.

References

- 1 Bircher J, Muller J, Guggenheim P, Haemmerli VP. Treatment of chronic portal-systemic encephalopathy with lactulose. *Lancet* 1966; 1: 890-3.
- 2 Conn HO, Lieberthal MM. *The hepatic coma syndromes and lactulose*. Baltimore: Williams and Wilkins, 1979.
- 3 van Velthuisen JA. Food additives derived from lactose; lactitol and lactitol palmitate. *J Agric Food Chem* 1979; 27: 680-6.
- 4 Bircher J, Buhrer M, Franz K, van Velthuisen JA. Erstmalige Anwendung von Lactitol in der Behandlung der porto-systemischen Enzephalopathie. *Schweiz Med Wochenschr* 1982; 112: 1306-7.
- 5 Conn HO. Trailmaking and number-connection tests in the assessment of mental state in portal systemic encephalopathy. *Am J Dig Dis* 1977; 22: 541-50.
- 6 Kendrick DC, Gibson AJ, Moyes ICA. The revised Kendrick battery: Clinical studies. *Br J Soc Clin Psychol* 1979; 18: 329-39.
- 7 Wechsler D. *Wechsler adult intelligence scale manual*. New York: Psychological Corporation, 1955.
- 8 Bachmann C. Nitrogen metabolism. In: Richterich R, Colombo JP, eds. *Clinical chemistry*. Chichester: John Wiley, 1981: 398-401.
- 9 Wyper DJ, Lennox GA, Rowan JO. Two minute slope inhalation technique for cerebral blood flow measurement in man. I Method. *J Neurol Neurosurg Psychiatr* 1976; 39: 141-6.
- 10 Sherlock S, Summerskill WHJ, White LP, Phear EA. Portal systemic encephalopathy. Neurological complications of liver disease. *Lancet* 1954; 2: 453-7.
- 11 Zeegen R, Drinkwater JE, Dawson AM. Method of measuring cerebral dysfunction in patients with liver disease. *Br Med J* 1970; 2: 633-6.
- 12 Hoyumpa AM, Desmond PV, Avant GR, Roberts RK, Schenker S. Hepatic encephalopathy. *Gastroenterology* 1979; 76: 184-95.
- 13 Liehr H, Englisch G, Rasenaek U. Lactulose - a drug with antiendotoxin effect. *Hepatogastroenterology* 1980; 27: 356-60.
- 14 Kaupke C, Sprague T, Gitnick GL. Hypernatraemia after the administration of lactulose. *Ann Intern Med* 1977; 86: 745-6.