LACTULOSE IN THE TREATMENT OF ACUTE AND CHRONIC HEPATIC ENCEPHALOPATHY*

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and

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INTRODUCTION

Lactulose (1-4-beta-galactosidofructose), a synthetic disaccharide, has recently been used for the treatment of chronic hepatic encephalopathy, with encouraging results (Bircher *et al*, 1966; Fung *et al*, 1968; Rottiers *et al*, 1968; Lande *et al*, 1968; Ma *et al*, 1969 and Elkington *et al*, 1969). It has also been shown that lactulose acts, not by decreasing putrefactive bacteria in the intestines, but rather by 'acid dialysis' of the colon, resulting in both diminished colonic absorption and increased colonic excretion of ammonia and perhaps other toxic substances (Haemmerli and Bircher, 1969). The present report is a further assessment of lactulose therapy in the treatment of both acute and chronic hepatic encephalopathy and is an extension of a preliminary study reported previously (Fung *et al*, 1968). The results of the present study were obtained in a clinical trial carried out in the last 2½ years.

METHOD

Patients presenting with overt clinical evidence of acute hepatic encephalopathy were used in this study. To those cases who had evidence of chronic hepatic encephalopathy, as manifested by recurrent episodes of acute hepatic encephalopathy, long-term lactulose therapy was given. The parameters used for the diagnosis and assessment of hepatic encephalopathy were: (1) disorientation; (2) Coma (graded I to IV)—Coma I = mild mental changes like memory loss, intellectual deterioration and altered sleep rhythm, Coma II=definite drowsiness (pre-coma), Coma III = unconscious but responds to pain, Coma IV = unconscious and no response to pain; (3) flapping tremor; (4) constructional apraxia (Fig. 1) and whenever possible (5) electroencephalographic evidence of encephalopathy (Fig. 2). These parameters were assessed daily and recorded.

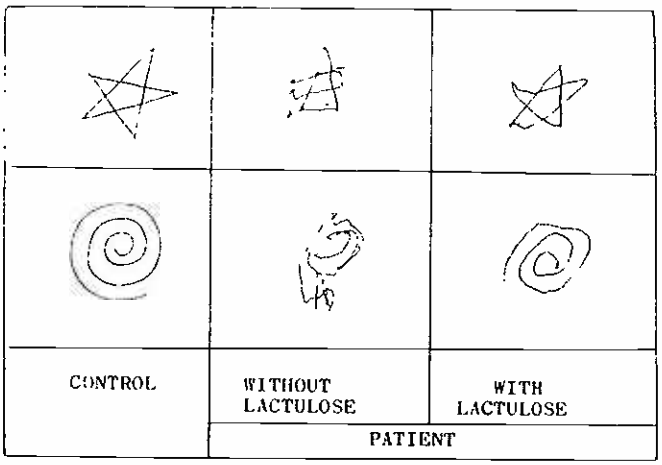

Fig. 1. Effect of lactulose on the constructional apraxia of acute hepatic encephalopathy. Note the marked improvement with lactulose therapy.

RESULTS AND DISCUSSION

The clinical, biochemical and histological data of the 11 cases are shown in Table I. Most of the cases were in their fifties or sixties and the majority were males and Chinese. Ten of the 11 cases had evidence of cirrhosis of the liver (4 alcoholic and 6 cryptogenic). In addition, 2 of the cases had hepatocellular carcinoma. The diagnosis of cirrhosis was based on histological evidence but when this was not available, it was based on clinical evidence like jaundice, hepatosplenomegaly, ascites, oesophageal varices, spider naevi, liver palms (palmar erythema) and biochemical evidence like marked hypoalbuminaemia.

All cases had evidence of acute hepatic encephalopathy before lactulose was given (Table II). Lactulose was then started at a dose of 30 mls. t.d.s. The dose was regulated to give 3 to 4 soft stools per day. In 6 cases (1 to 5 and 11) lactulose produced definite improvement without colonic washout or protein restriction. In 2 cases (6 and 8) lactulose, with protein restriction but without colonic washout, produced improvement. In 1 case (10) lactulose, with colonic washout and

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*Read in the Symposium on Hepatic Coma, 4th World Congress of Gastroenterology, Copenhagen, 13th July, 1970.

TABLE I. CLINICAL, BIOCHEMICAL AND HISTOLOGICAL DATA OF THE CASES IN THIS STUDY.

CASE No	AGE yrs.	SEX	RACE	CLINICAL DIAGNOSIS	HEPATO-MEGALY	SPLENO-MEGALY	SPIDER NAEVI	LIVER PALMS	ASCITES	LIVER FUNCTION TESTS					LIVER HISTOLOGY
										S.BIL.	S.A.P	S.Alb.	S.Glob	SGPT	
1	55	M	Ind.	ALCOHOLIC CIRRHOSIS	2cm.	0	0	0	+	3·2	20·4	1·9	4·8	280	NIL
2	48	M	Ind	ALCOHOLIC CIRRHOSIS	2cm.	5cm.	0	+	0	2·9	12·0	2·0	4·5	325	CIRRHOSIS
3	53	M	Ch	ALCOHOLIC CIRRHOSIS, DIABETES MELLITUS.	3cm	3cm	+	+	+	5·2	12·8	1·8	5·5	408	NIL
4	48	M	Ch	CRYPTOGENIC CIRRHOSIS. HYPERTENSION.	5cm	3cm.	+	+	0	1·2	5·6	3·5	5·0	225	NIL
5	54	M	Ch	CRYPTOGENIC CIRRHOSIS. PORTO-CAVAL SHUNT FOR BLEEDING OESOPHAGEAL VARICES.	3cm.	3cm	+	0	0	1·6	18·0	2·9	4·5	133	CIRRHOSIS
6	61	F	Eur	LEPTOSPIROSIS WITH HEPATO-RENAL FAILURE.	8 cm.	0	0	0	+	30·0	14·8	2·6	3·5	172	NIL
7	59	M	Ch.	ALCOHOLIC CIRRHOSIS	3cm.	0	+	0	+	18·7	18·0	2·2	5·5	245	CIRRHOSIS, HEPATOMA
8	69	M	Ch.	CRYPTOGENIC CIRRHOSIS	0	0	+	+	+	4·8	8·4	1·9	4·8	138	NIL
9	65	M	Ch.	CHOLELITHIASIS, CHOLANGITIS, CIRRHOSIS.	4cm.	0	0	+	0	27·6	46·6	2·7	3·5	275	NIL
10	55	M	Ch.	CRYPTOGENIC CIRRHOSIS, AORTIC STENOSIS	5cm.	0	+	+	+	6·8	34·0	2·9	3·9	>400	CIRRHOSIS. HEPATOMA
11	68	F	Ch.	CRYPTOGENIC CIRRHOSIS	3cm.	0	0	+	+	2·1	7·5	2·6	2·9	237	NIL

M = MALE; F = FEMALE; Ind. = INDIAN; Ch. = CHINESE; Eur. = EURASIAN; + = PRESENT; 0 = ABSENT, HEPATOSPLENOMEGALY IN cm. BELOW SUBCOSTAL MARGIN; S. BIL = S.BILIRUBIN (mg.%); S.A.P. = S. ALKALINE PHOSPHATASE (K.A. UNITS); S.Alb. = S. ALBUMIN (gm %); S.Glob = S. GLOBULIN (gm.%); SGPT = S.GLUTAMIC PYRUVIC TRANSMINASE (KING UNITS).

TABLE II. RESULTS OF LACTULOSE THERAPY IN ACUTE HEPATIC ENCEPHALOPATHY.

CASE No.	EVIDENCE OF HEPATIC ENCEPHALOPATHY					TREATMENT			RESULTS OF LACTULOSE THERAPY					
	DISORIENTATION	COMA I-IV	FLAPPING TREMOR	CONST. APRAXIA	E E G.	LACTULOSE (T.D.S.)	C/W	PROTEIN INTAKE (PER DAY)	DISORIENTATION.	COMA I-IV	FLAPPING TREMOR	CONST. APRAXIA	E E G	CONCLUSION
1	+	I	+	+	ABNORMAL	30 mls.	0	70 gms.	0	0 3rd. DAY	0 6th. DAY	0 6th. DAY	NORMAL	IMPROVED
2	+	I	+	+	ABNORMAL	30 mls.	0	70 gms.	0	0 4th DAY	0 4th. DAY	0 4th. DAY	NORMAL	IMPROVED
3	+	I	+	+	NIL	30 mls	0	70 gms.	0	0	0	0 5th DAY	NORMAL	IMPROVED
4	+	0	+	+	NIL	30 mls	0	70gms.	0	0	0	0 7th. DAY	NIL	IMPROVED
5	+	I	+	+	NIL	20 mls.	0	70gms.	0	0	0	0	NIL	IMPROVED
6	+	II	+	+	ABNORMAL	30 mls	0	0-20gms.	0	0 3nd DAY	0 14th. DAY	0	IMPROVED	IMPROVED
7	+	0	+	+	ABNORMAL	30 mls	0	0-20gms.	+	III 2nd DAY	+ 2nd DAY	+	WORSEN	FAILURE
8	+	I	+	+	ABNORMAL	30 mls	0	20 gms.	0	0 2nd. DAY	0 3rd. DAY	0 5th. DAY	IMPROVED	IMPROVED
9	0	I	+	+	NIL	30 mls. + NEOMYCIN	+	0 gm.	+	III-IV	+	+	NIL	FAILURE
10	0	0	+	+	NIL	30 mls.	+	0-40gms.	0	0	0 2nd. DAY	0 5th. DAY	NIL	IMPROVED
11	0	I	+	+	NIL	30 mls.	0	70gms.	0	0	0 8th. DAY	IMP.	NIL	IMPROVED

E.E.G. = ELECTROENCEPHALOGRAM; C/W = COLONIC WASHOUT; + = PRESENT; 0 = ABSENT.

All the cases had evidence of acute hepatic encephalopathy before lactulose therapy was started. Nine out of 11 cases showed improvement but improvement could be attributed directly to lactulose alone in 6 of the 11 cases i.e. 54·5%. Improvement could be evident as early as the second day of lactulose therapy.

protein restriction, produced improvement. Improvement was thus evident in 9 out of 11 cases (81·8%). However, as 2 of these cases had concomitant protein restriction, and 1 case had both protein restriction and colonic washout in addition to lactulose therapy, and since improvement might have been due to these additional measures, improvement could be attributed directly to lactulose alone in only 6 out of the 11 cases (54·5%). There was failure in 2 cases (7 and 9) followed by death in terminal hepatic coma. Closer analysis however show that in Case 7 nothing could possibly have saved him since he had hepatocellular carcinoma in addition to cirrhosis, while in Case 9, the liver failure was terminal and all measures including neomycin, colonic washout, protein-free diet and glucose were without any effect. In the cases that improved, improvement occurred as early as the second day of lactulose therapy.

Seven of the 11 cases had evidence of chronic hepatic encephalopathy and were given lactulose on a long-term basis. Five of these 7 cases had prior neomycin therapy, thus enabling comparison of lactulose with neomycin therapy. Table III shows that initial improvement was present in all cases (100%). However, sustained long-term improvement was seen in only 5 of the 7 cases (71·4%). In these 5 cases, lactulose was more effective than neomycin since it abolished all evidence of encephalopathy better than neomycin and in the face of a normal protein intake. This allowance of normal protein intake is an important advantage over neomycin since cirrhotic patients are often in negative nitrogen balance already. Four of these 5 cases are still alive and well on long-term lactulose therapy, while 1 case (2) succumbed to bleeding oesophageal varices after being well on lactulose for 1 year. In the other 2 cases (8 and 10) there was initial improvement which was maintained for 6 weeks in Case 8 and 3 weeks in Case 10. They eventually died, Case 10 probably from the bleeding oesophageal varices while Case 8 was in terminal stages of his liver failure. In both these cases all measures including neomycin, colonic washout, protein-free diet and glucose were without any effect.

An example of the abolition of constructional aparaxia by lactulose therapy is shown in Fig. 1. Improvement of the EEG with lactulose can be seen in Fig. 2. A diagramatic representation of the effect of neomycin therapy and lactulose therapy on the chronic hepatic encephalopathy of Case 1 is shown in Fig. 3.

TABLE III. LONG-TERM LACTULOSE THERAPY IN THE TREATMENT OF CHRONIC HEPATIC ENCEPHALOPATHY AND COMPARISON WITH NEOMYCIN THERAPY.

CASE No.	NEOMYCIN THERAPY					LACTULOSE THERAPY						FINAL OUTCOME
	DURATION	PROTEIN INTAKE (PER DAY)	COMA	FLAPPING TREMOR	CONST. APRAXIA	DURATION	PROTEIN INTAKE (PER DAY)	COMA	FLAPPING TREMOR	CONST. APRAXIA	CONCLUSION	
1	4 MONTHS	0-20gms.	0	+	+	28 MONTHS	70 gms.	0	0	0	MORE EFFECTIVE THAN NEOMYCIN.	ALIVE & WELL ON LACTULOSE
2	5 MONTHS	20 gms.	0	+	0	12 MONTHS	70 gms.	0	0	0	MORE EFFECTIVE THAN NEOMYCIN.	DIED OF BLEEDING OESOPHAGEAL VARICES
3	2 MONTHS	0-20gms.	0	0	0	20 MONTHS	70 gms.	0	0	0	EFFECTIVE	ALIVE & WELL ON LACTULOSE
4	1 MONTH	0-20gms.	0	0	+	4 MONTHS	70 gms.	0	0	0	MORE EFFECTIVE THAN NEOMYCIN	ALIVE & WELL ON LACTULOSE.
5	1 WEEK	0-20gms.	0	+	+	5 WEEKS	70gms.	0	0	0	MORE EFFECTIVE THAN NEOMYCIN	ALIVE & WELL ON LACTULOSE
8	TERMINAL 2 DAYS	0 gms.	+	+	+	6 WEEKS	20-70 gms.	0→+	0→+	0→+	FAILURE AFTER INITIAL IMPROVEMENT.	DIED OF HEPATIC FAILURE.
10	TERMINAL 5 DAYS	0 gms.	+	+	+	3 WEEKS	40-70 gms.	0→+	0→+	0→+	FAILURE AFTER INITIAL IMPROVEMENT.	DIED OF HEPATIC FAILURE AND BLEEDING VARICES

+ = PRESENT; 0 = ABSENT.

As 5 cases had prior neomycin therapy, it was possible to compare lactulose with neomycin. With lactulose therapy all cases had initial improvement but sustained longterm improvement was seen in only 5 of the 7 cases i.e. 71·4%. In these 5 cases, lactulose was superior to neomycin since it abolished all evidence of encephalopathy better than neomycin and also in the face of normal protein intake.

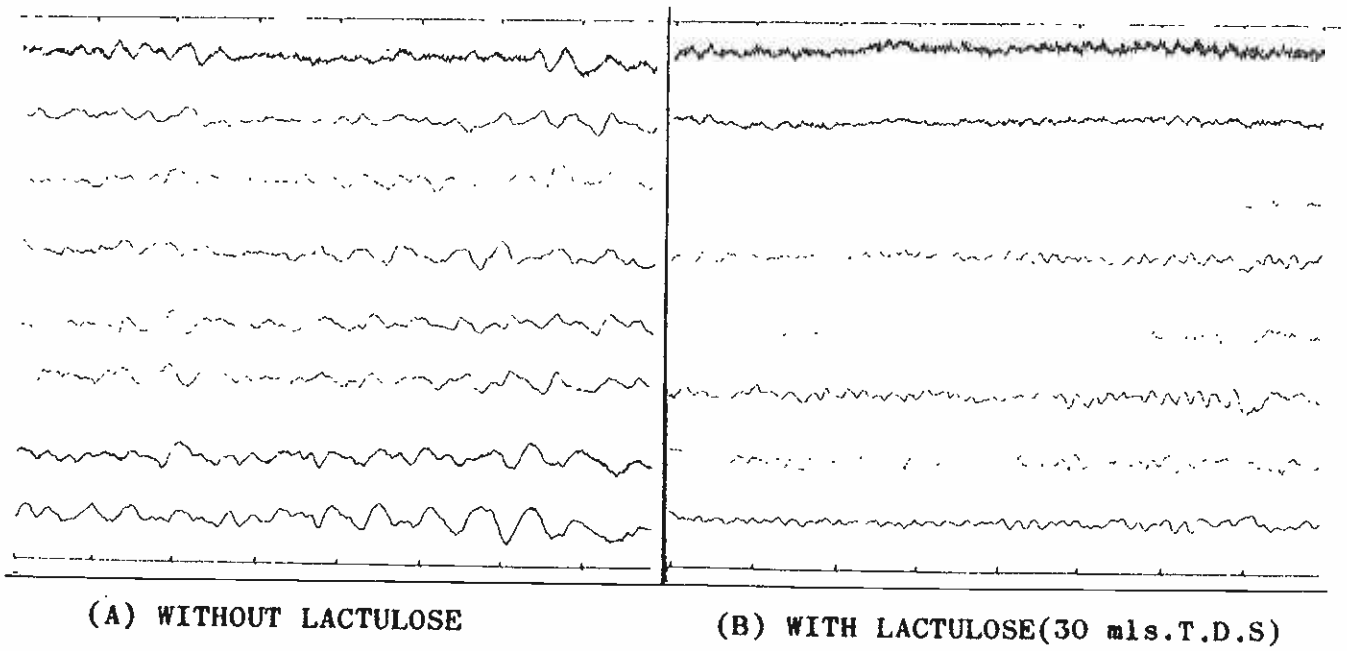

Fig. 2. Effect of lactulose on the electroencephalogram in acute hepatic encephalopathy. Note the slow waves indicating encephalopathy in (A) before lactulose was started and the marked improvement in (B) when lactulose was given.

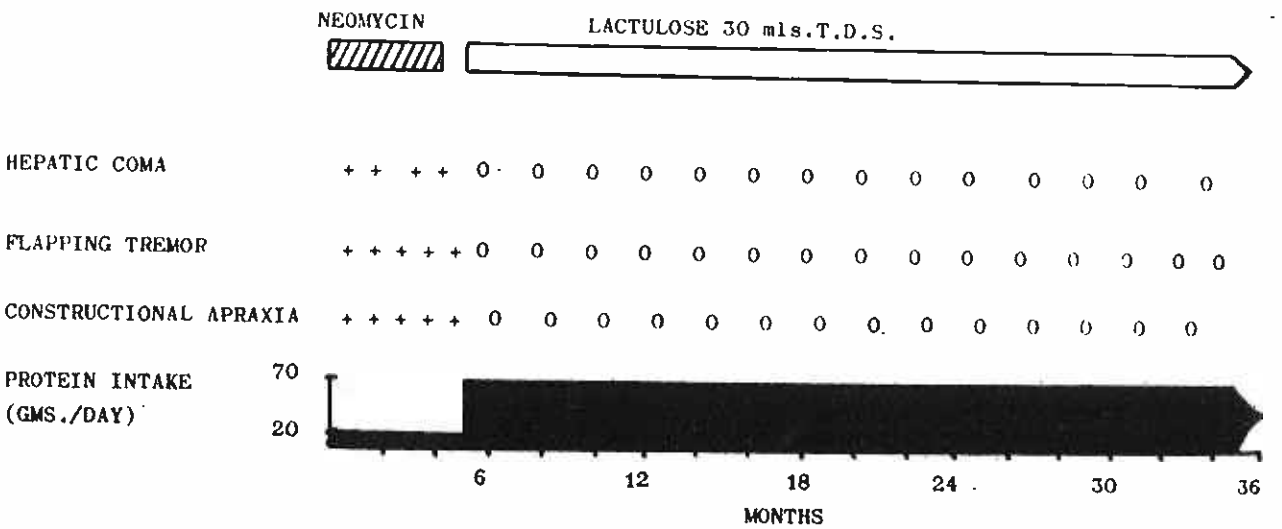

Fig. 3. Treatment of chronic hepatic encephalopathy in Case 1. Comparison of neomycin therapy with lactulose therapy. Note the persistence of occasional Coma I, flap and constructional apraxia during neomycin therapy and complete abolition of these when lactulose was started. This improvement was sustained in spite of normal protein intake. The case remains well.

SUMMARY

Eleven cases with evidence of acute hepatic encephalopathy were treated with lactulose. There was improvement in 81·8% but this could be attributed directly to lactulose alone in 54·5% of cases. In the 7 cases with chronic hepatic encephalopathy, initial improvement was seen in all (100%) with lactulose therapy. This improvement was maintained by long-term lactulose therapy in 5 of the 7 cases (71·4%). Lactulose was found to be more effective than neomycin. In terminal stages of liver failure both neomycin and lactulose were ineffective even if combined with all other measures. It is concluded that lactulose is useful and effective in the treatment of both acute and chronic hepatic encephalopathy and is more effective than neomycin.

ACKNOWLEDGEMENT

The authors are grateful to Dr. A. L. Gwee for the EEGs in Cases 6, 7 and 8; to Dr. Wesselius de Casparis and Dr. K. S. Liem for helpful advice and to N. V. Philips-Duphar for the supply of lactulose.

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