Comparative modes of action of lactitol and lactulose in the treatment of hepatic encephalopathy

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SUMMARY   Lactitol, an unabsorbed sugar with defined laxative threshold and superior taste properties has been suggested as an alternative to lactulose in the treatment of hepatic encephalopathy. In the present study we have compared the colonic metabolism of the two sugars using an *in vitro* faecal incubation system. Both sugars were readily metabolised by faecal bacteria producing volatile fatty acids and the metabolism was inhibited by neomycin. The effect of lactitol and lactulose on terminal ileal and colonic pH was monitored in six normal subjects using a radiotelemetry technique. Both sugars significantly lowered right colonic pH (basal -6.51 ± 0.48 *vs* lactitol -5.63 ± 0.50; lactulose -5.18 ± 0.82, $p<0.05$). The pH of rest of the colon and terminal ileum was unaffected. Neomycin given concurrently with lactulose abolished acidification of right colon. As lactitol and lactulose have similar effects within the colon, lactitol would appear to have a role in the treatment of hepatic encephalopathy. As neomycin antagonises the effect of lactitol in the colon, its concurrent use may be less effective in the treatment of hepatic encephalopathy.

Lactulose, an unabsorbed disaccharide (1:4, B-galactosido-fructose) has been extensively used in the treatment of hepatic encephalopathy.[1 2] Lactulose, however, is excessively sweet and consequently is unacceptable to some patients. Lactitol (B-galactosido-sorbitol), a disaccharide analogue of lactulose has recently been described.[3] This sugar is highly water soluble, less sweet than lactulose and is not absorbed in the human small intestine.[4] It has seemed to us therefore that lactitol might have a potential as an alternative therapeutic agent to lactulose in the treatment of hepatic encephalopathy. A recent open clinical trial[5] supports this suggestion as lactitol appeared to be as effective as lactulose in the management of patients with this condition.

In the present study experiments were designed to characterise the colonic metabolism of lactitol. In the first, an *in vitro* faecal incubation system was developed to simulate anaerobic fermentation of lactitol by human faecal bacteria. In the second, the effects of lactulose and lactitol on ileal and colonic pH *in vivo* were compared using a radiotelemetry device in normal human subjects.

The combination of neomycin and lactulose is still used in the treatment of hepatic encephalopathy despite the theoretical possibility that neomycin may inhibit the bacterial metabolism of lactulose. We have therefore taken the opportunity of investigating the effect of neomycin on colonic lactulose metabolism *in vitro* and *in vivo*.

Methods

COLONIC BACTERIAL METABOLISM OF LACTITOL IN VITRO

An *in vitro* culture system was developed to simulate as closely as possible the anaerobic metabolism of human colonic bacterial flora *in vivo*. A glass reservoir painted black externally to exclude light was used as the reaction chamber. Normal human volunteers passed approximately 25 g faeces into a beaker containing degassed water. The stool was immediately mixed with 500 ml nutrient medium in the reaction chamber which contained, NaCl 68

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mmol/l; KCl 5 mmol/l, a free L-amino acid mixture (0·47 mg amino acid nitrogen/l, Vamin N Kabivitrum Ltd), sodium taurocholate 10 mmol/l to inhibit growth of non-colonic bacteria and either lactitol or lactulose 20 g/l. The reaction mixture was stirred continuously and maintained at 37°C. The surface of the mixture was continuously flushed with O_2 free N_2 to maintain anaerobicity. The colonic mucosa *in vivo* normally secretes HCO_3 ions[6] whereby the intraluminal pH of colon is maintained in the range of 6–7.[7] In the present system the pH of reaction mixture was maintained at 7·0 by continuous titration of 1 M/l NaOH using an autoburette (Radiometer, Copenhagen, Denmark).

In pilot studies, aliquots of freshly passed faeces and reaction mixture were cultured after 24 hour incubation. Cultures from the reaction mixtures showed the presence of both aerobic and anaerobic organisms representative of those cultured from aliquots obtained from the same faecal samples before incubation.

Aliquots of samples (20 ml) were collected from the reaction chamber at 0 and 24 h incubation into a universal container maintained at 4°C, which was then immediately frozen and stored at −20°C until analysis of volatile fatty acids was carried out.

EXPERIMENTAL DESIGN

Stool samples from five normal human subjects were incubated with the lactitol containing medium, and separate stool samples from the same subjects incubated with lactulose containing medium. In three further experiments, stool samples were incubated with the lactulose containing medium and after establishing that bacterial fermentation was proceeding, as evidenced by titration requirements of NaOH to maintain pH at 7·0, neomycin was added in doses of 100, 300, and 500 mg respectively and incubation carried out for 24 hours as described above.

ANALYTICAL TECHNIQUE

The volatile fatty acid levels in the culture medium were measured by a modified gas liquid chromatography method as previously described.[8] The chromatograph used was a Pye Unicam 104 with a flame ionisation detector. Samples of the culture medium (1 ml) were mixed with 0·1 ml of concentrated HCl and 0·2 ml 50 mmol/l 3-methyl valeric acid (internal standard). The mixture was centrifuged and the supernatant (2 ul) injected into a column of 5% poly neopentyl glycol sebacate, 1% phosphoric acid and Anakrom A (80–100 mesh) packed in a 1·8× 0·002 m glass column (Field Instruments Co Ltd, Weybridge, Surrey) maintained at 110°C.

Standard curves were constructed by injecting calibrated amounts of a mixture of each volatile fatty acid and samples quantified from peak height measurement.

Lactic acid was measured as previously described[9] with a standard lactate dehydrogenase kit (Boehringer Mannheim Ltd, London).

EFFECT OF LACTULOSE AND LACTITOL ON TERMINAL ILEAL AND COLONIC pH

Six healthy volunteers all members of the department gave their informed consent and participated in a randomised crossover study. The study was approved by the Ethical Committee of Brent Area Health Authority. pH sensitive radiotelemetry capsules (Remote Control Systems Ltd, London) were calibrated in standard buffer solutions at 37°C and then swallowed. The capsules were allowed to pass through the intestine and pH recordings were obtained for five to 10 minute periods every one to two hours. The full details of the technique used to measure intraluminal pH by radiotelemetry have been described previously.[10] Initially the site of capsule was determined by occasional radiographic screening. In later studies we found that the capsule could be satisfactorily localised by identifying the site of maximum signal strength and then following the pH changes along its course. The capsule remained in the caecum for six to 24 hours and the passage of capsule from terminal ileum into caecum was characterised by a sudden and sustained fall in pH which enabled us to identify its entry from terminal ileum into the caecum. Mean values of repeated measurements of pH from terminal ileum, right colon, left colon and rectum were obtained. The rectum was identified by noting maximum signal strength on the lower sacrum or by recording the pH just before the capsule was passed. In only one study which was abandoned the pH capsule remained in the right colon for more than 36 hours. In all other studies it was possible to obtain the pH measurements in the terminal ileum, right colon, left colon, and rectum. In majority of cases the pH of freshly passed stool was also measured.

EXPERIMENTAL DESIGN

The subjects were randomly assigned to receive a normal diet, or this supplemented with lactulose and lactitol. Both sugars were consumed for three to four days in increasing doses so as to produce two to three semiformed motions/24 h. The final doses of lactulose and lactitol administered were 30–80 g/24 h and 40–180 g/24 h in two to four divided daily doses. All subjects undertook normal daily activities and each study period was separated by at least seven days to allow normalisation of colonic bacterial flora and bowel habit.

In three of the subjects, the lactulose study was

repeated as described except that neomycin at a dose of 0·5 to 1·0 g three to four times a day was also administered.

The statistical differences of intraluminal pH changes were assessed using the paired *t* test.

Results

1 COLONIC BACTERIAL METABOLISM OF LACTITOL AND LACTULOSE IN VITRO
The titration requirement of NaOH to maintain pH 7·0 during lactitol incubation was 103+33 mmol/24 h (mean+SD; n=5) and 152+22 mmol/24 h during lactulose incubation. The volatile fatty acids identified during both incubation studies were acetic acid, propionic acid, butyric acid, and lactic acid. The concentrations of volatile fatty acids liberated during the 24 hour incubation period are summarised in Table 1.

When neomycin at doses of 100 and 300 mg was added to lactulose containing medium, the titration requirements were 140 and 130 mmol NaOH/24 h. At a dose of 500 mg however, lactulose metabolism appeared almost completely inhibited for 24 hours and the reaction had a titration requirement of only 10 mmol NaOH/24 h.

2 EFFECT OF LACTITOL AND LACTULOSE ON TERMINAL ILEAL AND COLONIC pH
In the control experiments there was a significant fall in pH between the terminal ileum (7·51+0·37) and right colon (6·51+0·48; p<0·01). The pH values found in the right colon, left colon and rectum were similar to those previously described[7] and are shown in Table 2.

There was a significant fall in right colonic pH during ingestion of lactitol to 5·63+0·54 (p<0·05) and lactulose to 5·18+0·82 (p<0·01). The values obtained during the ingestion of the two sugars were, however, not significantly different. Neither sugar had a significant effect on the luminal pH of the terminal ileum, left colon or the faeces.

When lactulose was administered with neomycin, the pH profile of the terminal ileum, right colon, left colon, rectum and faeces as shown in Table 2 were not significantly different from those recorded during the control experiments.

Discussion

Lactitol is produced by hydrogenation of lactose and should soon be available as a pure, crystalline powder which is highly soluble in water. With a sweetness of 35% compared with sucrose, its taste properties are considerably superior to its analogue lactulose. Recent intestinal perfusion experiments have shown that lactitol is neither hydrolysed nor absorbed intact by the human small intestine.[1] Further studies have shown that a substantial proportion of orally ingested lactitol is metabolised *in vivo* and the estimated caloric value of this sugar has been found to be approximately 2–3 kcal/g (Grimble *et al*, unpublished data). The disparity between the results of small intestinal perfusion experiments and the *in vivo* caloric utilisation studies suggested that the colon was the major site of lactitol metabolism. As lactitol also acts as an osmotic cathartic agent,[4] we wondered whether this sugar might have a place in the treatment of hepatic encephalopathy. The results of the *in vitro* culture experiments clearly show that human faecal bacteria, under anaerobic conditions, utilise lactitol as an energy substrate and that it was the release of volatile fatty acids that lowered the pH of the reaction mixture. Lactitol was metabolised in a similar manner to lactulose with acetic acid being the predominant volatile fatty acid produced in both cases. There are no published studies to compare our data of *in vitro* lactitol metabolism by colonic bacteria. A previous study of lactulose metabolism by colonic bacteria, however, suggested that lactic acid was the predominant metabolite produced.[11] This study, however, was carried out using pure cultures of different species of faecal bacteria and not the mixtures of species that are found in the faeces.

The similarity of handling of lactulose and lactitol by human faecal organisms in our *in vitro* culture system prompted us to compare the effects of the two sugars on the luminal pH of the terminal ileum, colon, rectum as well as faecal pH *in vivo*. The pH profiles of the terminal ileum, and colon were found to be very similar to those reported by Bown *et al* who used the same experimental technique.[7] We have confirmed that lactulose when ingested in sufficient doses to produce two to four semi-formed motions a day lowers the pH of the right colon and no significant changes being noted in pH in the other regions of the colon, terminal ileum or faeces. The present findings show that lactitol has an exactly similar effect to that of lactulose on colonic pH.

Table 1 *Concentration of volatile fatty acids (mmol/l) produced after 24 h faecal incubation*

	Lactitol	*Lactulose*
Acetic acid	40±13	74±22
Propionic acid	13±4	15±6
Butyric acid	23±16	2±1
Lactic acid	1±1	2±1

(Mean±SD. n=5).

Table 2   *Effect of lactulose and lactitol on pH of terminal ileum, colon and faeces*

	n	Terminal ileum	Right colon	Left colon	Rectum	Faeces
Basal	6	7·51±0·37	6·51±0·48*	6·33±0·72	6·53±0·69	6·07±0·31
Lactulose	6	7·23±0·44	5·18±0·82†	5·67±1·03	5·93±1·40	5·72±1·67
Lactitol	6	7·08±0·41	5·63±0·54‡	6·12±0·63	6·58±0·40	6·54±0·46
Lactulose+neomycin	3	7·3 ±0·41	6·4 ±0·96	6·4 ±0·6	6·2 ±0·4	

*Terminal ileum *vs* right colon p<0·001; †Basal *vs* lactulose p<0·01; ‡Basal *vs* lactitol p<0·05. Values are mean±SD.

There are a number of explanations as to why the change in luminal pH induced by the two sugars occurs only in the right side of the colon. Firstly the luminal concentration of unabsorbed sugars will be high in the proximal colon. Therefore it is likely to be the major site of bacterial fermentation, producing maximum concentration of volatile fatty acids and consequently lowering the pH. Secondly, the volatile fatty acids are avidly absorbed from the colonic mucosa,[12][13] so that their effect on luminal pH will diminish as luminal contents move distally. Finally it is known that bicarbonate ions are secreted into the lumen of the colon against both chemical and electrical gradients[6][14] which will neutralise the acid.

The exact mechanisms whereby lactulose exerts its beneficial effect on hepatic encephalopathy are not fully understood. Available evidence suggests that lactulose acts by influencing the ammonia metabolism in the intestine.[16–19] Ammonia is absorbed by non-ionic diffusion[15] and it has been suggested that ammonia absorption is reduced as a consequence of conversion of ammonia to the ionised form in acid media.[16] Such an explanation appears to be supported by studies that have measured ammonia concentrations in portal vein radicals during acidification of colon.[17] Studies on ammonia loss in the faeces, however, have not shown the expected increase.[20][21] Vince *et al*[18] claim that net ammonia production is decreased after ingestion of unabsorbed sugar, firstly by facilitating growth of anaerobic bacteria and incorporating ammonia into bacterial proteins and secondly lowering the pH will inhibit the growth of proteolytic organisms.[22] Finally it has been suggested that the cathartic effect of lactulose may serve to both reduced ammonia production and absorption. Whatever may be the mechanism whereby lactulose exerts its beneficial effect on hepatic encephalopathy, the present *in vitro* and *in vivo* studies show that lactitol is handled in the colon in a strikingly similar fashion to lactulose. Lactitol has superior taste properties and it is tolerated better by patients.[5] We would therefore suggest that this sugar has potential as an alternative to lactulose in the treatment of hepatic encephalopathy.

The combination of lactulose and neomycin is often used in the treatment of hepatic encephalo-pathy on the basis presumably that the combination of the two is superior to using either drug alone. Although there are several studies showing that lactulose and neomycin when used on their own are equally effective in the treatment of hepatic encephalopathy,[19][23–25] there are no controlled clinical trials showing that combination therapy is superior to the use of either drug on its own.[1] During the course of the present study we took the opportunity of examining the effect of neomycin on the colonic metabolism of lactulose both *in vitro* and *in vivo*. The findings show that neomycin inhibits the bacterial metabolism of lactulose *in vitro* and negates the effect of lactulose on right sided colonic pH. Our findings therefore not only question the validity of combination therapy in hepatic encephalopathy, but raise the distinct possibility that neomycin might actually inhibit the beneficial effect of lactulose in this condition.

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