Cite this article as: BMJ, doi:10.1136/bmj.38048.506134.EE (published 30 March 2004)

Papers

Non-absorbable disaccharides for hepatic encephalopathy: systematic review of randomised trials

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Abstract

Objective To assess the effects of non-absorbable disaccharides (lactulose and lactitol) in patients with hepatic encephalopathy.
Data sources Cochrane Hepato-Biliary Group controlled trials register, Cochrane Library, Medline, and Embase until March 2003; reference lists of relevant articles; authors and pharmaceutical companies.
Review methods Randomised trials that compared non-absorbable disaccharides with placebo, no intervention, or antibiotics for hepatic encephalopathy were included. The primary outcome measures were no improvement of hepatic encephalopathy and all cause mortality.
Results 22 trials were included. Compared with placebo or no intervention, non-absorbable disaccharides seemed to reduce the risk of no improvement in patients with hepatic encephalopathy (relative risk 0.62, 95% confidence interval 0.46 to 0.84, six trials). However, high quality trials found no significant effect (0.92, 0.42 to 2.04, two trials). Compared with placebo or no intervention, non-absorbable disaccharides had no significant effect on mortality (0.41, 0.02 to 8.68, four trials). Non-absorbable disaccharides were inferior to antibiotics in reducing the risk of no improvement (1.24, 1.02 to 1.50, 10 trials) and lowering blood ammonia concentration (weighted mean difference 2.35 µmol/l, 0.06 µmol/l to 13.45 µmol/l, 10 trials). There was no significant difference in mortality (0.90, 0.48 to 1.67, five trials).
Conclusions There is insufficient evidence to support or refute the use of non-absorbable disaccharides for hepatic encephalopathy. Antibiotics were superior to non-absorbable disaccharides in improving hepatic encephalopathy, but it is unclear whether this difference is clinically important. Non-absorbable disaccharides should not serve as comparator in randomised trials on hepatic encephalopathy.

Introduction

Hepatic encephalopathy is a complex neuropsychiatric syndrome, which may complicate acute or chronic liver failure.[1] It is characterised by changes in mental state including a wide range of neuropsychiatric symptoms ranging from minor signs of altered brain function to deep coma.[2]

Treatment of hepatic encephalopathy aims at reducing the production and absorption of ammonia, which is involved in the pathogenesis.[3 4] As colonic bacteria are the primary source of ammonia, treatment initially consisted of poorly absorbed antibiotics, especially neomycin.[5 6] This treatment was implemented without appropriate scientific documentation. Lactulose was introduced as a safer alternative.[3] On the basis of two small trials,[5 6] lactulose was considered to be as effective as neomycin. Subsequent trials and meta-analyses concluded that lactitol and lactulose were equally effective.[7–10] Since the 1980s, non-absorbable disaccharides (lactulose and lactitol) have been considered as the standard treatment for hepatic encephalopathy.[11 12] Recent guidelines state that lactulose is the first line pharmacological treatment for hepatic encephalopathy.[12] Antibiotics can be considered a therapeutic alternative to non-absorbable disaccharides in acute hepatic encephalopathy but in chronic encephalopathy should be reserved for patients who respond poorly to non-absorbable disaccharides.[12]

We performed a systematic review to assess the beneficial and harmful effects of non-absorbable disaccharides for hepatic encephalopathy and to compare them with antibiotics.

Methods

The review was performed according to a published protocol[13] and reported according to the QUOROM statement.[14]

Searching

We searched the Cochrane Hepato-Biliary Group controlled trials register, the Cochrane Library, Medline, and Embase up to March 2003. Included terms were "hepatic encephalopathy or cirrhosis", and "lactulose, lactitol, or disaccharide", and "random* or clinical".[13] We screened bibliographies of relevant articles and conference proceedings and wrote to experts and pharmaceutical companies.

Selection—We included all randomised trials that compared non-absorbable disaccharides (lactulose and lactitol) with placebo, no treatment, or antibiotics for hepatic encephalopathy. Inclusion was regardless of publication status, language, or blinding. Included patients had acute, chronic, or minimal hepatic encephalopathy.

Validity assessment—Two reviewers independently assessed trial quality[15 16] by examining three components: generation of allocation sequence (classified as adequate if based on computer generated random numbers, tables of random numbers, or similar), concealment of allocation (classified as adequate if based on central randomisation, sealed envelopes, or similar), and blinding (classified as adequate if the trial was described as double blind or had blinded outcome assessment).[13] We classified trials with adequate concealment of allocation and adequate blinding as high quality.

Data abstraction—Two reviewers (BA-N and LLG) independently extracted data from each trial. Our primary outcome measures were the numbers of patients without improvement of hepatic encephalopathy and all cause mortality. Improvement was defined as partial or complete resolution of clinical or

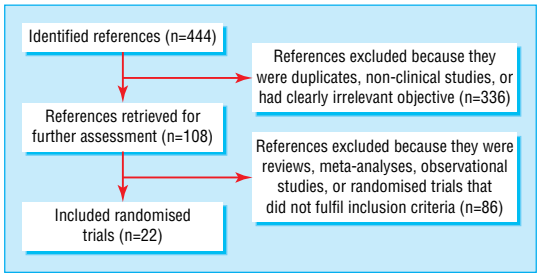

Fig 1 Selection process of eligible randomised trials from all identified references

subclinical symptoms of hepatic encephalopathy. Secondary outcome measures were adverse events, number connection test result, and blood ammonia concentration. In the number connection test, participants are instructed to connect numbers printed on a page consecutively from 1 to 25 as quickly as possible. The test score is the time the patient needs to perform the test, including the time needed to correct any errors. A low score represents a good performance. All outcomes were assessed at the end of treatment and maximum follow up.

Trial characteristics—We extracted the type and cause of the underlying liver disease, type of hepatic encephalopathy (acute, chronic, or minimal); mean age; proportion of men; number of patients randomised to each intervention arm; type, dose, and duration of treatment; mode of administration; trial quality[15 16]; trial design (parallel or crossover); duration of follow up; and number of dropouts. We sought data on all patients, irrespective of compliance or follow up. Primary investigators were contacted if data were missing.

Quantitative data synthesis—All data were analysed on the basis of intention to treat, including all randomised patients irrespective of compliance or follow up. If patients had missing outcome data, we carried forward the last reported observed response.[17] Data from the first period of crossover trials were included. Binary outcomes were expressed as relative risks with 95% confidence intervals. Continuous outcomes were expressed as weighted mean difference with 95% confidence intervals. We used a random effects model[18] because we anticipated clinical variability between trials. Statistical heterogeneity was explored by the χ^2 test with significance set at $P<0.1$. Potential sources of heterogeneity were explored through subgroup analyses with regard to the quality of methods and type of hepatic encephalopathy. We used the test of interaction[19] to compare the difference between the estimates of subgroup analyses. Analyses were performed in Review Manager version 4.2.2. for Windows and SPSS version 11.0 for Windows.

Results

Figure 1 summarises the literature search. We included 22 trials that assessed lactulose or lactitol versus placebo, no treatment, or antibiotics.[5 6 20–39] Two trials were published as abstracts.[32 37] The remaining were published as full articles. Eighteen trials used a parallel group design and four a crossover design. All trials were described as randomised, but adequate generation of the allocation sequence was described in only four.[22 30 31 39] Treatment allocation was adequately concealed in 10 trials,[5 6 20–23 26 30 36 39] double blinding was reported in 15 trials,[5 6 20–25 27 32–34 36 38 39] and one trial had blinded outcome assessment.[30] We classified nine trials as high quality.[5 6 20–23 30 36 39]

Lactulose or lactitol *v* placebo or no intervention

Ten trials with 280 patients (75% men) assessed lactulose or lactitol versus placebo or no intervention (table 1).[20–29] All patients had cirrhosis and acute,[25] chronic,[20 22–24] acute or chronic,[21] or minimal hepatic encephalopathy.[26–29] Eight trials assessed oral lactulose,[20–24 26 28 29] one assessed oral lactitol,[27] and one assessed lactitol enemas.[25] The daily mean doses of lactulose ranged from 30 g to 84 g (median 50 g). In six trials the dose was adjusted to obtain two to three semisoft stools per day. The median duration of treatment was 15 days (range 5 to 360 days). None of the trials followed up patients after the end of treatment.

Trial results were homogeneous. Compared with placebo or no intervention, lactulose and lactitol seemed to reduce the risk of no improvement of hepatic encephalopathy (relative risk 0.62, 95% confidence interval 0.46 to 0.84, six trials; fig 2). This result was not robust when trials were stratified by quality. High quality trials found no significant effect of lactulose or lactitol on the risk of no improvement (0.92, 0.42 to 2.04, two trials; fig 2), whereas low quality trials found a significant beneficial effect of lactulose or lactitol (0.57, 0.40 to 0.83, four trials; fig 2). Although this difference in treatment response was not significant ($P=0.3$ by test of interaction), it is noteworthy that the event rate in the control groups was significantly associated with quality of methods (high quality trials 38%, low quality trials 78%; $P=0.0005$ with χ^2 test). The event rate in the experimental group was not significantly different in trials with high (35%) and low (43%) quality ($P=0.5$ with χ^2 test). The treatment responses in acute, chronic, and minimal hepatic encephalopathy did not differ significantly. However, there was no significant effect of lactulose or lactitol on

Table 1 Randomised trials of non-absorbable disaccharides versus placebo or no intervention in treatment of patients with hepatic encephalopathy

	Study design	Quality*	No of patients randomised	Type of hepatic encephalopathy	Experimental/control intervention	No of patients without improvement/total†		No of dropouts/total	
						Experimental	Control	Experimental	Control
Elkington 1969[20]	Crossover	High	7	Chronic	Lactulose/sorbitol	‡		Not described	
Simmons 1970[21]	Parallel	High	26	Acute + chronic	Lactulose/glucose	4/14	5/12	3/14	2/12
Rodgers 1973[22]	Crossover	High	6	Chronic	Lactulose/sorbitol	‡		3	
Germain 1973[23]	Parallel	High	18	Chronic	Lactulose/saccharose	4/9	3/9	None	
Corazza 1982[24]	Parallel	Low	32	Chronic	Lactulose/placebo	§		Unknown	
Uribe 1987[25]	Parallel	Low	15	Acute	Lactitol enemas/tap water enemas	0/10	4/5	Unknown	
Watanabe 1997[26]	Parallel	Low	36	Minimal	Lactulose/no treatment	12/22	11/14	2/22	1/14
Shi 1997[27]	Parallel	Low	31	Minimal	Lactitol/glucose	§		Unknown	
Li 1999[28]	Parallel	Low	86	Minimal	Lactulose/no treatment	22/48	27/38	Unknown	
Dhiman 2000[29]	Parallel	Low	26	Minimal	Lactulose/no treatment	6/14	12/12	4/14	4/12

*Classified with adequate allocation concealment and adequate blinding as high quality.
†Improvement defined as partial or complete resolution of clinical or subclinical symptoms of hepatic encephalopathy.
‡Lactulose and sorbitol reported to be equally effective, but numerical data not available.
§Lactulose/lactitol reported to be superior to placebo, but numerical data not available.

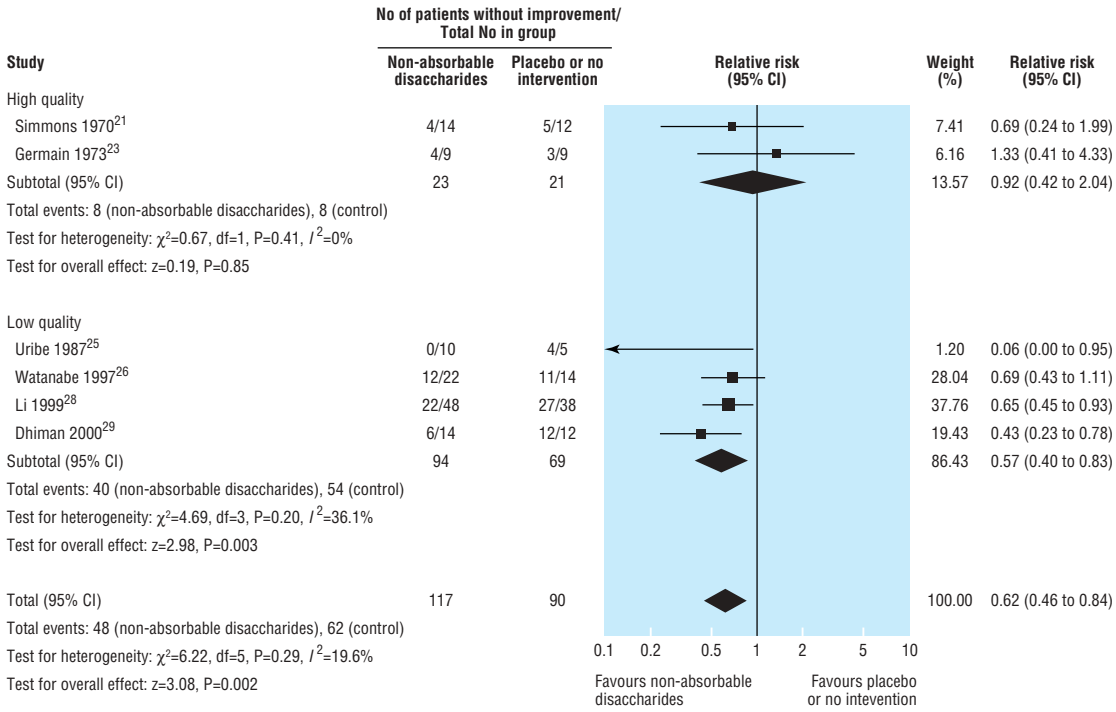

Fig 2 Number of patients without improvement of hepatic encephalopathy in trials on non-absorbable disaccharides versus placebo or no intervention, stratified according to quality of methods

acute (0.27, 0.02 to 3.28, two trials) or chronic hepatic encephalopathy (1.33, 0.41 to 4.33, one trial). Trials in patients with minimal hepatic encephalopathy found that lactulose or lactitol significantly reduced the risk of no improvement assessed by various psychometric tests (0.61, 0.47 to 0.79, three trials). These trials were all of low methodological quality.

Compared with placebo or no intervention, lactulose and lactitol had no significant effect on mortality (0.41, 0.02 to 8.68, four trials) or the number connection test result (weighted mean difference −9.0 seconds, −20.1 to 2.1, one trial) but tended to lower blood ammonia (−8.16 µmol/l, −16.44 µmol/l to 0.18 µmol/l, four trials). Data on adverse events were incompletely reported. Most trials mentioned adverse events associated only with non-absorbable disaccharides. We were therefore unable to perform a reliable meta-analysis of this outcome. None of the reported adverse events were serious, and all originated from the gastrointestinal tract (diarrhoea, flatulence, abdominal pain, or nausea).

Lactulose or lactitol versus antibiotics

Twelve trials with 698 patients (72% men) assessed lactulose or lactitol versus antibiotics (table 2).[5 6 30–39] All patients had cirrhosis and acute,[6 32 39] chronic,[5 31 35 36 38] acute or chronic,[30] or presumed chronic hepatic encephalopathy.[33 34 37] Nine trials assessed oral lactulose,[5 6 30 31 33–37] and three trials assessed oral lactitol.[32 38 39] The daily mean dose of lactulose ranged from 30 g to 120 g (median 59 g) and of lactitol from 30 g to 60 g (median 60 g). The antibiotics were neomycin,[5 6 30] ribostamycin,[31] vancomycin,[32] or rifaximin.[33–39] The median duration of treatment was 15 days (range 5-90 days). One trial assessed all outcomes 15 days after the end of treatment,[38] and one reported mortality 28 days after the end of treatment.[39] All other trials followed the patients only to the end of treatment.

Trial results were homogeneous. Compared with antibiotics, patients taking lactulose or lactitol had a significantly higher risk of no improvement of hepatic encephalopathy (1.24, 1.02 to 1.50, 10 trials; fig 3). We found no significant difference in response to treatment between aminoglycosides and rifaximin (P = 0.2 by test of interaction) or when trials were stratified by quality or type of hepatic encephalopathy. We found no significantly different effect on mortality between non-absorbable disaccharides and antibiotics (0.90, 0.48 to 1.67, five trials) or on adverse events (1.62, 0.57 to 4.58, eight trials). None of the reported adverse events were serious, and all originated from the gastrointestinal tract (diarrhoea, flatulence, abdominal pain, or nausea). Compared with antibiotics, patients on lactulose or lactitol took on average six more seconds to complete the number connection test (weighted mean difference 6.4 seconds, 1.4 seconds to 11.3 seconds, six trials) and had higher blood ammonia concentrations (2.35 µmol/l, 0.06 µmol/l to 4.64 µmol/l, 10 trials).

Discussion

We did not find sufficient evidence to determine whether lactulose or lactitol have a significant beneficial effect on patients with hepatic encephalopathy. In our overall analysis non-absorbable disaccharides seemed to improve encephalopathy, but this effect was seen in only low quality trials.

The beneficial effect in low quality trials was related to significantly worse rates of improvement in the control group. This finding concurs with empirical evidence showing that low quality trials exaggerate the beneficial effects of treatment.[15 16 40] Accordingly, the overall result may reflect bias because of the low methodological quality of most of the included trials. Our results may also be inflated by publication bias.

We found no significant effect of non-absorbable disaccharides on acute or chronic hepatic encephalopathy. Only low quality trials in patients with minimal hepatic encephalopathy found that lactulose had a beneficial effect, as assessed by various

Table 2 Randomised trials on non-absorbable disaccharides versus antibiotics in treatment of patients with hepatic encephalopathy

	Study design	Quality*	No of patients randomised	Type of hepatic encephalopathy	Experimental/control intervention	No of patients without improvement/total†		No of dropouts/total	
						Experimental	Antibiotics	Experimental	Antibiotics
Conn 1977[5]	Crossover	High	33	Chronic	Lactulose + placebo/neomycin + sorbitol	3/18	2/15	None in 1st period	
Atterbury 1978[6]	Parallel	High	47	Acute	Lactulose + placebo/neomycin + sorbitol	4/23	4/24	1/23	1/24
Orlandi 1981[30]	Parallel	High	190	Acute + chronic	Lactulose/neomycin + magnesium sulfate	63/91	48/82		17§
Russo 1989[31]	Crossover	Low	15	Chronic	Lactulose/ribostamycin	1/8	2/7	Unknown	
Blanc 1993[32]	Parallel	Low	60	Acute	Lactitol/vancomycin	9/29	10/31	2/29	2/31
Bucci 1993[33]	Parallel	Low	58	Unknown	Lactulose + placebo/rifaximin + sorbitol	‡		Unknown	
Fera 1993[34]	Parallel	Low	40	Unknown	Lactulose + placebo/rifaximin + placebo	4/20	0/20	Unknown	
Festi 1993[35]	Parallel	Low	21	Chronic	Lactulose/rifaximin	‡		Unknown	
Massa 1993[36]	Parallel	High	40	Chronic	Lactulose + placebo/rifaximin + sorbitol	2/20	0/20	Unknown	
Song 2000[37]	Parallel	Low	64	Unknown	Lactulose/rifaximin	7/25	8/39	1/25	1/39
Loguercio 2003[38]	Parallel	Low	27	Chronic	Lactitol + placebo/rifaximin + placebo	11/13	6/14	3/13	2/14
Mas 2003[39]	Parallel	High	103	Acute	Lactitol + placebo/rifaximin + placebo	12/53	10/50	7/53	8/50

*Classified with adequate allocation concealment and adequate blinding as high quality.
†Improvement defined as partial or complete resolution of clinical or subclinical symptoms of hepatic encephalopathy.
‡Experimental and control intervention reported to be equally effective but numerical data not available.
§Exact number of dropouts in each intervention group not reported and accordingly it was not possible to perform intention to treat analysis for this trial.

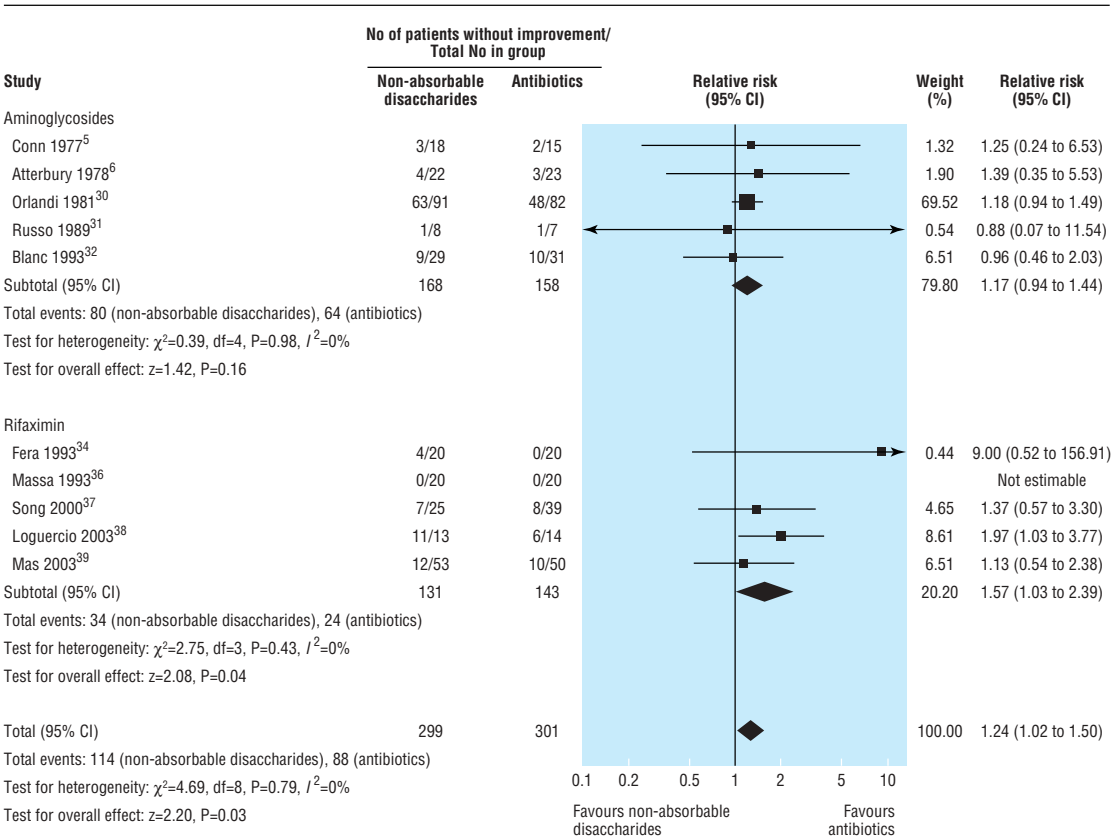

Fig 3 Number of patients without improvement of hepatic encephalopathy in trials on non-absorbable disaccharides versus antibiotics, stratified according to type of antibiotic

non-validated psychometric tests. The clinical relevance of these tests is uncertain.[41]

Lactulose has been used as the standard treatment for hepatic encephalopathy, and its efficacy has been considered to be beyond doubt.[2 7 24 25 42] However, when it was introduced, the few trials that compared lactulose against placebo found no beneficial effect of lactulose.[21 23] It was implemented in clinical practice because two trials found it "equally effective" to neomycin,[5 6] which had been the standard treatment for hepatic encephalopathy since 1957.[43] There are two major pitfalls in this reasoning. Firstly, the efficacy of neomycin in hepatic encephalopathy has never been shown. We identified only one randomised trial that compared neomycin with placebo[44] and one that compared neomycin plus lactulose with placebo,[45] both for acute hepatic encephalopathy. Both trials found no significant beneficial effects of neomycin. Secondly, lactulose was considered as equally effective to neomycin because event rates in intervention groups were not significantly different.[5 6] However, lack of statistical significance does not imply that treatments have equal effects.[46] Both trials were small,[5 6] and neither reported sample size calculations based on an equivalence hypothesis or stated a margin of equivalence.[46 47] It would require a far larger sample size than these two trials (a total of 78 patients) to establish with confidence that lactulose and neomycin have comparable effects.

Later on, new trials compared other antibiotics to non-absorbable disaccharides for hepatic encephalopathy. None was set up as an equivalence trial. Sample size calculations with statements implying an equivalence hypothesis or a margin of equivalence were not reported in any of the trials. All were underpowered to show equivalence. Nevertheless, all trials concluded equivalence from the lack of statistical significance.[30–39] It seems that the research was continuously building up on both insufficient evidence and inadequate methods. Our analyses indicate that antibiotics are statistically superior to non-absorbable disaccharides in improving hepatic encephalopathy and lowering blood ammonia concentrations. However, it is unclear whether the effects are clinically important. Considering this, the lack of effect of antibiotics in placebo controlled trials,[44 45] the risk of multiresistance,[48] and the potential risk of severe adverse events[5] lead us to conclude that there is insufficient evidence to recommend the use of antibiotics for hepatic encephalopathy.

Mechanisms

When assessing intervention effects for hepatic encephalopathy, it is important to consider the fluctuating course as well as the impact of treating precipitating factors in acute hepatic encephalopathy. Well conducted placebo controlled trials on the use of ornithine aspartate in patients with minimal or chronic hepatic encephalopathy[49 50] and lactulose plus neomycin[45] in those with acute hepatic encephalopathy found improvement rates in the placebo group ranging from 40% to 70%. Many clinicians claim to have witnessed beneficial effects of non-absorbable disaccharides on patients with hepatic encephalopathy. This effect may represent a high rate of spontaneous improvement and successful treatment of precipitating factors.

Implications

Non-absorbable disaccharides seem to have been introduced into clinical practice without appropriate documentation. This leads to at least three major problems. Firstly, patients are given a treatment of uncertain efficacy. It might be beneficial; it might be unfavourable. Secondly, there is reluctance towards performing randomised trials to assess lactulose or lactitol versus placebo because it is considered unethical. Thirdly, most randomised trials on new treatments for hepatic encephalopathy use lactulose as comparator. New treatments are considered effective if improvement rates do not differ significantly from the group treated with lactulose, although trials are vastly underpowered to show equivalence. This approach is most problematic. Non-absorbable disaccharides should not serve as comparator in randomised trials on hepatic encephalopathy until other trials have shown that lactulose or lactitol has any beneficial effect on hepatic encephalopathy.

What is already known on this topic

Non-absorbable disaccharides are considered standard treatment for hepatic encephalopathy

Non-absorbable disaccharides serve as control treatment in most trials of new drugs for hepatic encephalopathy

What this study adds

There is insufficient evidence to determine whether non-absorbable disaccharides are of benefit to patients with hepatic encephalopathy

Antibiotics seem superior to non-absorbable disaccharides in improving hepatic encephalopathy, but it is unclear whether this difference is clinically important

Non-absorbable disaccharides should not be used as the comparator in randomised trials on hepatic encephalopathy

We thank the patients who took part in the reviewed trials; the researchers who provided us with additional information; Jørgen Hilden, department of biostatistics, University of Copenhagen, for statistical support; and Peter Gøtzsche, Nordic Cochrane Centre, for valuable comments on an earlier draft of this review. This review is an abbreviated version of a Cochrane systematic review. The full version will be published in the Cochrane Library 2004, Issue 2. Cochrane Reviews are regularly updated as new evidence emerges and in response to comments and criticisms, and the Cochrane Library should be consulted for the most recent version of the review.

Contributors: BA-N drafted the protocol and paper, performed the literature searches, identified trials, extracted data, and performed the statistical analyses. LLG identified trials and extracted data. All reviewers contributed to the writing of the protocol and review and all have approved of the final version. BA-N is guarantor.

Funding: Danish Centre for Evaluation and Health Technology Assessment (DACEHTA), Danish Medical Research Council, and Copenhagen Hospital Corporation's Medical Research Council.

Competing interests: None declared.

Ethical approval: Not required.

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(Accepted 20 February 2004)

doi 10.1136/bmj.38048.506134.EE

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