

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 $\mu\text{mol/l}$, 0.06 $\mu\text{mol/l}$ to 13.45 $\mu\text{mol/l}$, 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}

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 protocol¹³ 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. 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. 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 subclinical symptoms of hepatic encephalopathy. Secondary outcome measures were adverse events, number connection test, 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



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end of treatment and maximum follow up. Primary investigators were contacted if data were missing.

Quantitative data synthesis—All data were analysed on the basis of intention to treat. Binary outcomes were expressed as relative risks. Continuous outcomes were expressed as weighted mean difference. Statistical heterogeneity was explored by the χ^2 test with significance set at $P < 0.1$. Subgroup analyses stratified trials by quality (high or low) and by type of hepatic encephalopathy.

Results

We included 22 trials that assessed lactulose or lactitol versus placebo, no treatment, or antibiotics.^{5 6 17–36} 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.^{19 27 28 36} We classified nine trials as high quality.^{5 6 17–20 27 33 36}

Lactulose or lactitol *v* placebo or no intervention

Ten trials with 280 patients (75% men) assessed lactulose or lactitol versus placebo or no intervention.^{17–26} All patients had cirrhosis and acute,²² chronic,^{17 19–21} acute or chronic,¹⁸ or minimal hepatic encephalopathy.^{23–26} Eight trials assessed oral lactulose,^{17–21 23 25 26} one assessed oral lactitol,²⁴ and one assessed lactitol enemas.²² 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 1). 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 1), whereas low quality trials found a significant beneficial effect of lactulose or lactitol (0.57, 0.40 to 0.83, four trials; fig 1). Although this difference in treatment response was not significant ($P = 0.3$ by test of interaction), it is noteworthy that the event rate (that is, the rate of no improvement) 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 treatment responses in acute, chronic, and minimal hepatic encephalopathy did not differ significantly. However, there was no significant effect of lactulose or lactitol on 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 (weighted mean difference -9.0 seconds, -20.1 to 2.1 , one trial) but tended to lower blood ammonia (-8.16 $\mu\text{mol/l}$, -16.44 $\mu\text{mol/l}$ to 0.18 $\mu\text{mol/l}$, four trials). Data on adverse events were

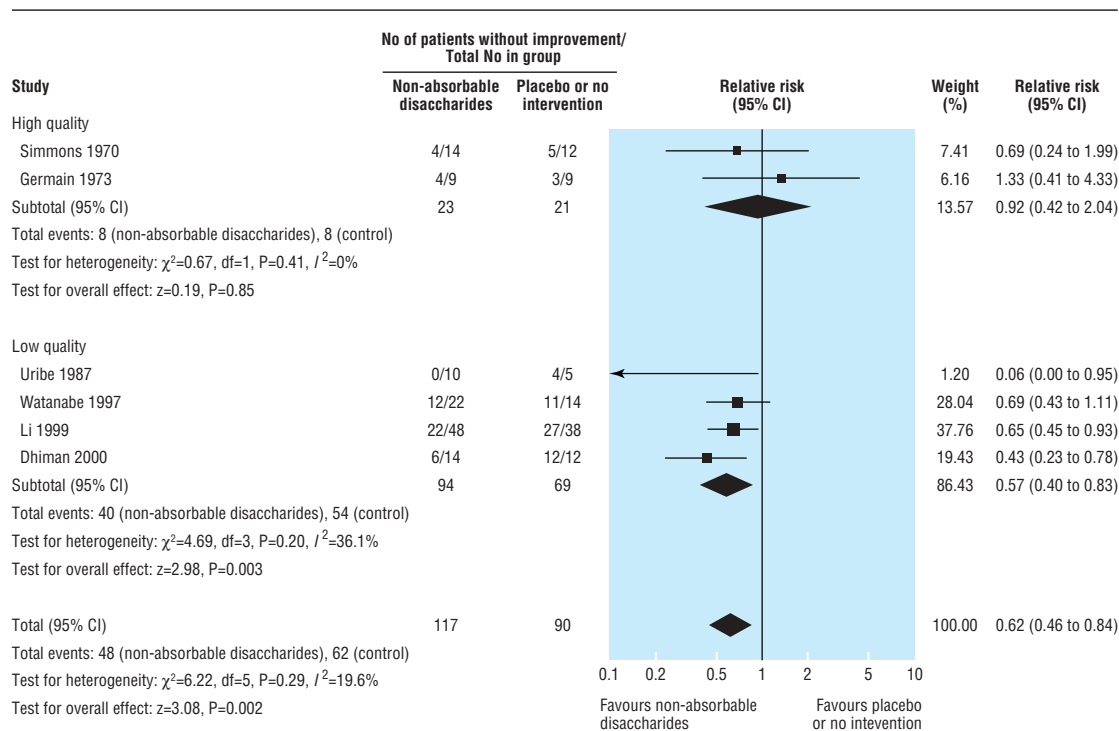


Fig 1 Number of patients without improvement of hepatic encephalopathy in trials on non-absorbable disaccharides versus placebo or no intervention, stratified according to quality of methods

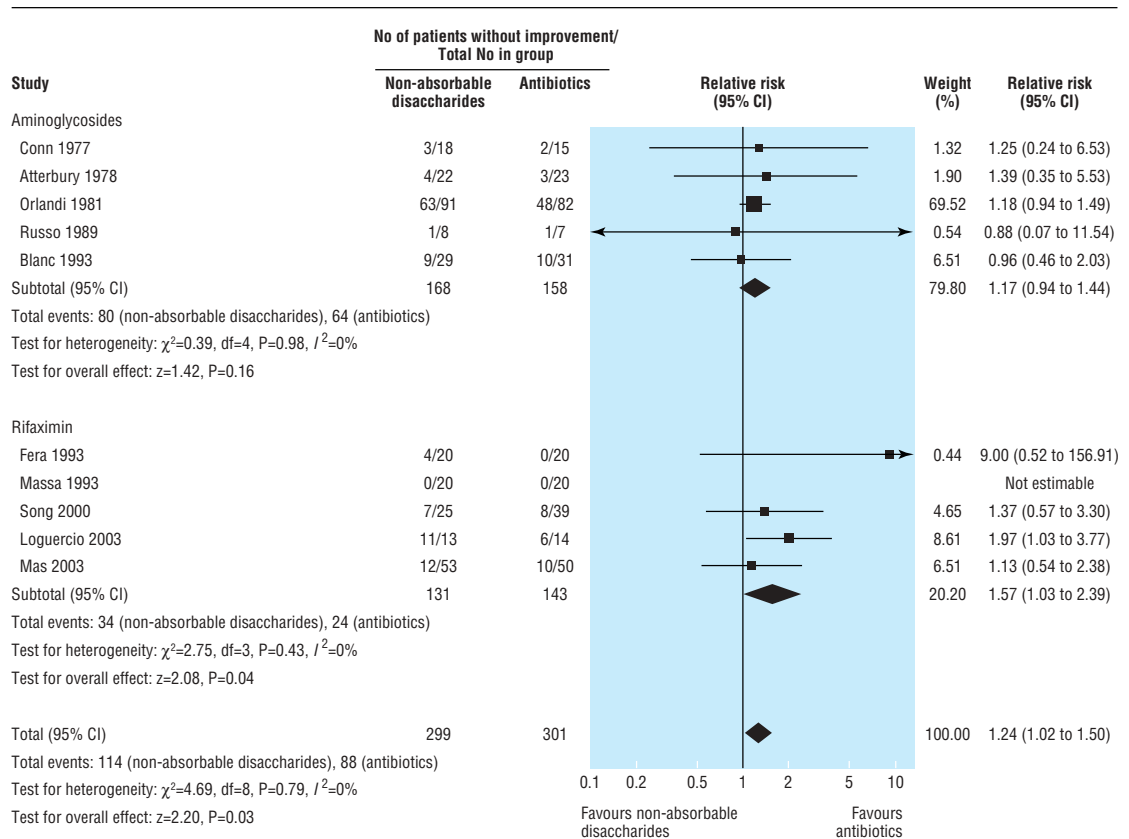


Fig 2 Number of patients without improvement of hepatic encephalopathy in trials on non-absorbable disaccharides versus antibiotics, stratified according to type of antibiotic

incompletely reported so we were 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.^{5 6 27-36} All patients had cirrhosis and acute,^{6 29 36} chronic,^{5 28 32 33 35} acute or chronic,²⁷ or presumed chronic hepatic encephalopathy.^{30 31 34} Nine trials assessed oral lactulose,^{5 6 27 28 30-34} and three trials assessed oral lactitol.^{29 35 36} 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 27} ribostamycin,³¹ vancomycin,³² or rifaximin.³⁰⁻³⁶ The median duration of treatment was 15 days (range 5-90 days). One trial assessed all outcomes 15 days after the end of treatment,³⁵ and one reported mortality 28 days after the end of treatment.³⁶ All other trials followed the patients only to the end of treatment.

Trial results were homogeneous. Compared with antibiotics, patients receiving lactulose or lactitol had a significantly higher risk of no improvement of hepatic encephalopathy (1.24, 1.02 to 1.50, 10 trials; fig 2). 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 $\mu\text{mol/L}$, 0.06 $\mu\text{mol/L}$ to 4.64 $\mu\text{mol/L}$, 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 37} 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 non-validated psychometric tests. The clinical relevance of these tests is uncertain.³⁸

Lactulose has been used as the standard treatment for hepatic encephalopathy, and its efficacy has been considered to be beyond doubt.^{2 7 21 22 39} However, when it was introduced, the few trials that compared lactulose against placebo found no beneficial effect.^{18 20} 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 1957.⁴⁰ 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 placebo⁴¹ and one that compared neomycin plus lactulose with placebo,⁴² 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, both trials were small,^{5 6} and neither reported sample size calculations based on an equivalence hypothesis or stated a margin of equivalence.^{33 44} 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.²⁷⁻³⁶ 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,^{41 42} the risk of multiresistance,⁴⁵ and the potential risk of severe adverse events⁵ lead us to conclude that there is insufficient evidence to recommend the use of antibiotics for hepatic encephalopathy.

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 not. Secondly, there is reluctance to perform 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

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

other trials have shown that lactulose or lactitol has any beneficial effect on hepatic encephalopathy.

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The acme of efficiency

In 1955 I was a registrar in a large mental hospital in the north of England. Most of the beds were in the old buildings, which had remained largely unchanged for nearly 100 years. There was also a modern building in the grounds, to which new patients were admitted. If these patients needed electroconvulsive therapy, they were anaesthetised and given a muscle relaxant. Electroconvulsive therapy was also widely used in the chronic wards, where it was the consequence of disturbed behaviour. There, it was given "straight"—that is, without anaesthetic or relaxant. This policy was defended by the view that the patients had never known anything different. However, one day, the medical superintendent came across an article which showed that a third of patients receiving straight electroconvulsive therapy had radiological evidence of vertebral compression fractures. He was appalled and immediately decreed that all patients receiving such therapy should have proper anaesthetic cover.

So, on the next occasion that an anaesthetist arrived, he was confronted, not with the dozen or so patients he had expected, but with 118. Unsurprisingly, he was somewhat put out, but, instead of complaining about lack of resources, he set about solving the problem. He had 10 beds set up in a small ward, and had the patients ushered in in groups of 10. They lay on the beds, and, armed with a 20 ml syringe of thiopentone, he gave each patient 3-4 ml. Of course, he had to draw the plunger back with each patient to be sure that he

was in a vein, so there was some mixing of the blood. I was perturbed because two of the patients had general paresis, but he assured me that patients with tertiary syphilis were not infectious. A nurse followed him, giving the scoline, and lastly I came with the ECT machine to give the fit. By the time all that was over, most of the patients were blue, or in some cases black, so a second nurse trundled round with an oxygen cylinder, giving oxygen to the most cyanosed patients.

The session was over in three hours, and all the patients were successfully treated. Nobody died, and, so far as I know, nobody acquired an infection, not even hepatitis. Of course, in those days, AIDS did not exist.

No doubt a present day manager would compliment the anaesthetist on his presence of mind and extreme efficiency.

Alan Gibson *retired consultant psychiatrist, Woking*

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