Rifaximin vs conventional oral therapy for hepatic encephalopathy: a meta-analysis

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CRD summary
This review concluded that rifaximin was similar to other oral therapies in its clinical efficacy for hepatic encephalopathy and it had fewer side-effects. This was a well-conducted review, but the reliability of the conclusions may be affected by the observed statistical variation and the lack of participant information.

Authors' objectives
To compare rifaximin with conventional oral therapy for hepatic encephalopathy.

Searching
Eight databases including PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE and CINAHL were searched up to December 2010, without publication status and language restrictions. Search terms were reported and reference lists of retrieved papers and reviews were searched.

Study selection
Randomised controlled trials were eligible for inclusion if they reported on the effectiveness of rifaximin, compared with non-absorbable oral disaccharides or other antibiotics, in patients with hepatic encephalopathy. Patients had to be older than 18 years, with a diagnosis of reversible neurological decline secondary to end-stage liver disease. The primary outcomes were the improvement in neurological function; the grade of hepatic encephalopathy, according to Conn's modification of the Parsons Smith classification; and safety. Secondary outcomes were the reduction in serum ammonia levels and changes in psychometric measures (mental status, asterixis [hand tremor], electroencephalograph characteristics and portosystemic encephalopathy sum) at the end of the treatment.

Most studies evaluated rifaximin 1,200mg per day in three doses; some evaluated 1,100mg in two doses. Control arms received non-absorbable oral disaccharides (lactulose 45 to 120mL per day or lactitol 60g per day) or antibiotic therapy (neomycin 3,000 or 4,500mg per day or paromomycin 1,500mg per day, in three doses). Most trials that used non-absorbable oral disaccharides aimed to induce several soft bowel movements per day, but none of them reported how they monitored their participants. Treatment duration ranged from seven days to six months.

Two reviewers independently assessed trials for inclusion.

Assessment of study quality
The quality of included trials was assessed using the Cochrane Collaboration's risk of bias tool, which covers the method of randomisation; allocation concealment; blinding of patients, caregivers and outcome assessors; and reporting of loss to follow-up and whether all patients were accounted for in the analysis and reporting. The assessment also covered the reporting of a sample size calculation and if this size was achieved; a clear definition of the primary outcomes; and if a crossover design was used.

The assessment was performed by two independent reviewers.

Data extraction
The proportions of patients with improvement in neurological function and common side-effects were extracted and used to calculate odds ratios with 95% confidence intervals. Mean differences were calculated for serum ammonia levels and psychometric measures along with 95% confidence intervals. Two independent reviewers extracted the data.

Methods of synthesis
Pooled odds ratios and weighted mean differences were obtained using random-effects meta-analysis with inverse-variance weighting. Statistical heterogeneity was assessed using $I^2$ and $X^2$ ($p<0.1$ indicated significant heterogeneity). The potential reasons for heterogeneity were explored. The data were analysed on an intention-to-treat basis and the last observation carried forward was used for patients with missing data. Only data from the first period of crossover trials were included. For the primary outcome, subgroup analyses were performed by control treatment regimen (oral...
disaccharides or antibiotics) and methodological quality.

**Results of the review**

Twelve trials were included in the review, with 565 patients (range 14 to 136). Five described the randomisation methods; eight had clearly reported allocation concealment; most had patient blinding to treatment; and six reported observer blinding to treatment. The methods for handling missing data, the descriptions of drop-outs, and power calculations were not adequately reported in any of the included trials.

**Neurological function**: Seven trials compared rifaximin with disaccharides and reported that both groups experienced either full resolution of hepatic encephalopathy or a clinically significant improvement, but there was no statistically significant difference between the groups. A similar result was seen in the five trials comparing rifaximin with antibiotics. In the combined analysis of all 12 trials, the results favoured rifaximin, but were not statistically significant (OR 1.96, 95% CI 0.94 to 4.08; I²=27%).

**Adverse events**: Patients receiving rifaximin had lower rates of diarrhoea (OR 0.20, 95% CI 0.04 to 0.92; eight trials; I²=66%), but the rates of abdominal pain, nausea, anorexia and weight loss were similar between the two groups. The combined analysis of all adverse events showed fewer events with rifaximin than with control (OR 0.27, 95% CI 0.12 to 0.59; nine trials; I²=69%).

**Serum ammonia**: Seven trials reported a statistically significant reduction in serum ammonia at the end of treatment in both groups. There was no statistically significant difference between the groups in the meta-analysis of all trials or of subgroups with disaccharides or antibiotics as the control. Statistical heterogeneity was very high for all serum ammonia analyses (I²=83% or more).

**Psychometric parameters**: Rifaximin improved electroencephalographic characteristics (WMD -0.21, 95% CI -0.33 to -0.09; four trials; I²=0) and portosystemic encephalopathy (WMD -2.33, 95% CI -2.68 to -1.98; three trials; I²=21%). There was no statistically significant difference between rifaximin and control for improvement in mental status and asterixis.

Trials with a high risk of bias were excluded from all analyses and the results remained consistent.

**Authors’ conclusions**

Rifaximin was similar to other oral therapies in its clinical efficacy for hepatic encephalopathy and it had fewer side-effects.

**CRD commentary**

This review specified clear inclusion criteria for the study design, interventions, participants and outcomes. A range of databases was searched, without language restrictions, reducing the risk of language and publication bias. The review methods, such as study selection, data extraction, and risk of bias assessment, were performed by two reviewers independently to reduce error and bias in these processes. An appropriate tool was used to assess the risk of bias and the results were fully reported for each trial. Suitable meta-analysis methods were used, but some of the pooled results should be treated with caution due to the high levels of heterogeneity.

This was a well-conducted review, but the reliability of the conclusions might be affected by the observed statistical heterogeneity and the lack of participant information.

**Implications of the review for practice and research**

**Practice**: The authors stated that due to its safety profile, rifaximin should be considered as a second option for hepatic encephalopathy in patients who failed to respond to disaccharide therapy, and as a first treatment for patients who were intolerant to disaccharides.

**Research**: The authors did not state any recommendations for research.

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