

Combination Therapy for the Treatment and Prevention of Hepatic Encephalopathy

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Request

Are there any clinical benefits associated with using combination therapy for the treatment and prevention of hepatic encephalopathy (HE) in patients with liver disease?

Response

BACKGROUND

HE is defined as a disorder of neuropsychiatric abnormalities due to acute or chronic hepatic insufficiency.^{1,2} HE is common in patients with cirrhosis, with symptoms noted in nearly 30-45% of this population. Minimal hepatic encephalopathy (MHE) is defined as patients with cirrhosis who have no clinical or electroencephalographic manifestations of HE but, when tested, will demonstrate neuropsychometric abnormalities.³

The management of HE involves use of medications that are targeted to reduce the accumulation of neurotoxic nitrogenous byproducts such as ammonia.^{1,2} The treatment of HE includes the use of oral antibiotics, nonabsorbable disaccharides, or probiotics. Currently, only rifaximin (HE prevention) and neomycin (HE treatment) are approved by the Food and

OBJECTIVE: To evaluate the efficacy and safety of combination therapy for the treatment and prevention of hepatic encephalopathy (HE).

DATA SOURCES: A PubMed MEDLINE search was conducted (1947-June 2012) using the key terms lactulose, lactitol, nonabsorbable disaccharide, metronidazole, rifaximin, neomycin, probiotics, and hepatic encephalopathy. Searches were limited to include articles published in English.

STUDY SELECTION AND DATA EXTRACTION: Study selection included published trials, case reports, and case series of humans with HE who were treated with combination therapy of rifaximin, lactulose, lactitol, metronidazole, neomycin, and/or probiotics.

DATA SYNTHESIS: Only 6 studies that evaluated the benefits of combination drug therapy in the treatment or prevention of HE were available for review. Four studies addressed the treatment of HE, 2 found no significant difference between lactulose/neomycin versus placebo or rifaximin/lactulose, 1 assessed the use of rifaximin/lactulose without a control group, and the fourth found no significant difference between lactulose/probiotics versus either drug alone, although each group showed improvement from baseline. In the 2 prevention trials, both of which stemmed from the same data, the combination of rifaximin/lactulose was superior to lactulose alone, showing significant improvement in mental status, blood ammonia levels, and health-related quality of life and reductions in HE recurrence and hospitalization. Currently, there are no available clinical studies evaluating dual antibiotic therapy, metronidazole with nonabsorbable disaccharides, or antibiotics with probiotics.

CONCLUSIONS: The evidence evaluating the use of combination therapy for the treatment of HE does not support its widespread use. The combination of rifaximin and lactulose may be considered in the treatment of HE and in patients refractory to monotherapy. The combination of rifaximin and lactulose should be considered for the prevention of HE, especially after the second episode of HE recurrence.

KEY WORDS: hepatic encephalopathy, lactitol, lactulose, metronidazole, neomycin, nonabsorbable disaccharide, probiotics, rifaximin.

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Drug Administration for this indication. Nonabsorbable disaccharides (lactulose and lactitol) are an alternative approach to reducing bacterial production and absorption of ammonia. No significant difference in efficacy has been shown between lactulose and lactitol, although most studies have used lactulose.³ Comparisons of lactulose to neomycin and rifaximin have resulted in similar rates of efficacy among the 3 agents.

No single product has been shown to be uniformly effective in the prevention or treatment of HE. Thus, combination therapy may be an option. The purpose of this review is to evaluate the efficacy and safety of combination therapy for the treatment and prevention of HE. Six clinical studies⁴⁻⁹

were identified that evaluated the efficacy of combination therapy for the treatment and prevention of HE (Table 1).

TREATMENT

Blanc et al.⁴ compared the combination of lactulose and neomycin (n = 40) to placebo (n = 40) in patients with cirrhosis and acute HE. The groups were similar at baseline in the degree of HE and serum ammonia concentrations. Most patients had HE precipitated by either gastrointestinal bleeding or infection. There was significant improvement of HE in each group compared to baseline. However, there

Table 1. Efficacy Studies of Combination Therapy for the Treatment and Prevention of Hepatic Encephalopathy

| Reference | Design | Dosing | Outcome |
|-------------------------------|---------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Treatment | | | |
| Blanc (1994) ⁴ | P, R, PC Acute HE and cirrhosis | Combination (n = 40): lactulose 30 g/day, titrated to 2-3 stools daily, and neomycin 500 mg 4 times/day Placebo (n = 40) Duration 5 days | HE improvement: 65% with combination vs 70% with placebo (p = NS) Blood ammonia (µmol/L): 112 ± 43 with combination vs 98 ± 36 with placebo group (p = NS) GI intolerance: 63% in combination group vs 7% in placebo group (p > 0.05) |
| Di Piazza (1991) ⁵ | P, double crossover Cirrhosis with chronic, permanent, or recurrent HE | Rifaximin 400 mg 3 times/day for 7 days Washout period Neomycin 500 mg 3 times/day for 7 days Rifaximin followed by neomycin (n = 8) Neomycin followed by rifaximin (n = 6) All pts. received lactulose 10-60/day, continued during washout Duration: 7 days | Clinical improvement (flapping, bradylalia, performance): rifaximin: 4 pts., neomycin: 0 pts. (p = NS) |
| Puxeddu (1995) ⁶ | P Grades 1, 2, and 3 HE | Combination (n = 55): rifaximin 400 mg 3 times/day and lactulose, titrated to 2-3 stools/day Duration: 15 days | Improvements in psychometric tests (p ≤ 0.001), blood ammonia levels (p < 0.05), and asterixis (p = 0.02) |
| Sharma (2008) ⁷ | P, R, controlled Cirrhosis with MHE | Group A (n = 35): lactulose Group B (n = 35): probiotics Group C (n = 35): lactulose and probiotics Lactulose dose 20-40 g/day, titrated to 2-3 stools daily Probiotics (<i>Streptococcus faecalis</i> 60 million, <i>Clostridium butyricum</i> 4 million, <i>Bacillus mesentericus</i> 2 million, lactic acid bacillus 100 million) 1 capsule 3 times/day Duration: 1 month | Psychometric test improvement: (p = 0.001 in all groups) Blood ammonia levels (µmol/L): group A: 102.3 ± 63.1 to 69.3 ± 33.3; group B: 108.2 ± 37.5 to 75.7 ± 33.0; group C: 96.3 ± 27.7 to 68.7 ± 28.4 (p < 0.05 in all groups) CTP class improvement: group A: 38.8%; group B: 40%; group C: 38% (p < 0.05 in all groups) Normalization of MHE parameters: group A: 54.8%; group B: 51.6%; group C: 56.6% (p ≥ 0.05 in all groups) |
| Prevention | | | |
| Bass (2010) ⁸ | P, DB, PC, R, MC Cirrhosis, recurrent HE (at least 2 overt HE episodes in past 6 months) | Combination (n = 140): rifaximin 550 mg 2 times/day with placebo Placebo (n = 159) Pts. (~90%) received lactulose (average daily dose ~30 g) Duration: 6 months or until therapy was discontinued | First breakthrough HE episode: 22.1% in combination group vs 45.9% in placebo group (HR 0.42, 95% CI 0.28 to 0.64; p < 0.001) First HE-related hospitalization: 13.6% with combination vs 22.6% with placebo (HR 0.50, 95% CI 0.29 to 0.87; p = 0.01) Adverse drug events and mortality similar between groups |
| Sanyal (2011) ¹⁰ | Parallel study with Bass (2010) ⁸ | | CLDQ scores: significantly higher with combination vs placebo (p < 0.05) Remission maintained: 74.2% with combination vs 50% with placebo |

CLDQ = Chronic Liver Disease Questionnaire; CTP = Child-Turcotte-Pugh; DB = double-blind; GI = gastrointestinal; HE = hepatic encephalopathy; HR = hazard ratio; MC = multicenter; MHE = minimal hepatic encephalopathy; P = prospective; PC = placebo controlled; R = randomized.

was no significant difference in efficacy between the groups and a significant increase in intolerance was shown with combination therapy compared to placebo. Management of precipitating causes of HE in the placebo group was associated with significant improvements in outcome variables, including serum ammonia concentration, electroencephalography, and intellectual function using the numbers connection test. There were 6 deaths in each group. The authors concluded that combination therapy with lactulose and neomycin should not be used in the treatment of HE because of the lack of benefit compared to placebo and the associated intolerance to therapy.

In a double-crossover study of 14 patients, Di Piazza et al.⁵ compared the use of rifaximin plus lactulose with neomycin plus lactulose for the treatment of HE. Results of initial therapy showed that patients who received rifaximin had greater improvement compared to baseline in performance (via linear analog patient self-assessment), asterixis, and bradylylia. However, the results were not statistically significant. Direct comparisons between neomycin and rifaximin showed favorable results with rifaximin versus neomycin, but the differences were not significant. The authors concluded that rifaximin plus lactulose was comparable to neomycin plus lactulose and may be considered for the treatment of chronic HE. The small number of patients included in the trial, despite the strength of the crossover design, may have precluded finding a significant difference.

In a prospective study, Puxeddu et al.⁶ evaluated the efficacy and tolerability of combination rifaximin and lactulose in 55 patients with HE. Most patients (80%) had grade 1 HE. Protein intake was restricted to 60–80 g daily. All patients showed improvement in HE and tolerated the treatment. By day 3, significant improvement was seen in mental status and blood ammonia levels. Time to response to therapy ranged from 1 to 11 days. The authors concluded that the combination of rifaximin and lactulose may be appropriate compared to aminoglycoside antibiotics for the management of HE. The trial was limited by having no control group.

In a prospective study, Sharma et al.⁷ evaluated the use of lactulose (n = 35), probiotics (n = 35), and the combination of lactulose and probiotics (n = 35) in patients with MHE and cirrhosis. Baseline characteristics were similar among the treatment groups. After 1 month of therapy, patients in all treatment groups had significant improvements in psychometric tests (p = 0.001), Child-Turcotte-Pugh class (p < 0.05), and reduction in blood ammonia levels (p < 0.05). The authors speculated that the failure of combination therapy to show greater efficacy over monotherapy might be the result of the cathartic or acidification effect of lactulose leading to early interference with the probiotic effect. In general, treatment regimens were well tolerated. The lack of benefit of the combination of lactulose and probiotic therapy suggests that its use is not worth the additional costs.

Prevention

In a prospective study, Bass et al.⁸ compared rifaximin (n = 140) to placebo (n = 159) for the prevention of HE. More than 90% of patients in each group were also receiving lactulose therapy. Rifaximin or placebo was continued for 6 months or until therapy was discontinued before that time. Compared to placebo, patients in the rifaximin group had significantly greater reductions in the first breakthrough HE episode (22.1% vs 45.9%) and the first HE-related hospitalization (13.6% vs 22.6%). Venous ammonia concentrations were measured at baseline and days 24, 84, and 168.9. The rifaximin group had a significantly greater decrease in ammonia concentrations compared to placebo (5.7 µg/dL vs 0.3 µg/dL, p = 0.039). Adverse drug events and mortality were similar in both groups. The authors concluded that rifaximin in combination with lactulose was effective in preventing breakthrough HE in patients with recurrent HE and cirrhosis.

In a concurrent study, the same investigators further evaluated the effect of rifaximin plus lactulose versus lactulose alone (placebo group) on health-related quality of life (HRQL) in 219 patients.¹⁰ The relationship between HRQL and breakthrough HE episode was also assessed. HRQL was measured by the Chronic Liver Disease Questionnaire (CLDQ) score. Results showed that patients who received rifaximin had significant improvement in CLDQ scores compared to the placebo group. Patients with HE breakthrough had significant reductions in CLDQ scores. The authors concluded that HRQL significantly improved in patients who received rifaximin in combination with lactulose and that worsening HRQL may predict HE events, irrespective of treatment.

Discussion

Inconsistent results regarding the efficacy of combination therapy in the management of HE highlight the difficulty of assessing therapy targeted at modulating mediators of HE. Overall management starts with reversing precipitating factors, which often leads to amelioration of HE. Thus, it has been suggested that placebo-controlled trials be conducted to determine the efficacy of what has been the gold standard of therapy, lactulose.¹¹ Nevertheless, the combination of rifaximin and lactulose for the treatment of HE evaluated in a small noncomparative trial showed significantly improved mental status and reduced blood ammonia levels.⁷ The study evaluating the combination of rifaximin and lactulose for the prevention of HE also demonstrated a significant reduction in HE recurrence and hospitalization and improvement in HRQL.^{8,10}

Neomycin, metronidazole, nonabsorbable disaccharides, and rifaximin are commonly used for the treatment of HE. Probiotics have been found to be as effective as lactulose in patients with stage 1 or 2 HE.^{12–15} Potential drug interac-

tions may contribute to the lack of efficacy seen with combination therapy. Probiotics may display susceptibility to antibiotics¹⁶ and studies evaluating the efficacy of this combination are lacking. Antibiotics may interfere with the bacterial metabolism of nonabsorbable disaccharides. Contrarily, the acidic environment created by nonabsorbable disaccharides may reduce the activity of some antibiotics.

Studies evaluating the combination of neomycin and lactulose for the treatment of HE produced conflicting results. Blanc et al. demonstrated no significant difference in the number of patients who recovered from HE with the combination compared to placebo while showing an increase in intolerability.⁴ However, this study had a small sample size, lacked statistical analyses, and had a short duration of therapy prior to evaluation (5 days). In a small crossover trial, Di Piazza et al. showed no significant difference between the combinations of rifaximin and lactulose versus neomycin and lactulose.⁵ The small sample size of this study may have precluded finding a significant difference, despite the strength of the crossover design.

Conversely, the combination of rifaximin and lactulose for the treatment of HE showed significant improvement in mental status and blood ammonia levels and significant reduction in HE recurrence and hospitalization.⁶ Although the Puxeddu et al. trial did not have a control group, its longer duration of evaluation (15 days) contributed to its success, with most patients responding between days 3 and 10.

The combination of probiotics with lactulose has been evaluated for the treatment of MHE and showed improvements in psychometric test, Child-Turcotte-Pugh class, and blood ammonia levels, but the results were similar compared to lactulose and probiotic monotherapy.⁷ Currently, there are no clinical studies evaluating the combination of antibiotics with other antibiotics, metronidazole with nonabsorbable disaccharides, and antibiotics with probiotics.

The combination of rifaximin and lactulose has emerged as viable regimen for the prophylaxis of HE.^{8,9} The strengths of the 2 evaluations performed from the prevention trial include the larger sample size, the greater power to detect a significant difference, and the design including a comparative control group.

The principal outcome desired in the management of HE is improvement in mental status. Studies have shown that improvement in HE is associated with a decrease in serum ammonia concentrations, consistent with the pathophysiology of HE. The disposition of blood ammonia is the balance between production and elimination; thus, while treatment may enhance elimination of ammonia, the net balance of ammonia may not be affected if production of ammonia (eg, through excessive protein ingestion) exceeds elimination. Consequently, the use of serum ammonia concentration monitoring may aid the clinician in evaluating therapy. Also, blood ammonia levels are primarily measured during acute HE and do not indicate whether pa-

tients will have significant improvement in preventing HE. Only 2 studies showed a significant improvement in blood ammonia levels as well as clinical improvement of HE with the combination group, especially rifaximin and lactulose, compared to monotherapy.^{8,10}

Additional trials are needed to evaluate combination therapy in the management of HE. A recent consensus statement was generated on the design and conduct of clinical trials.¹⁷ Because episodes of HE may resolve with management of the precipitating event, the consensus statement suggests that studies include a placebo group.

Based on the available studies evaluating combination therapy in the treatment and prevention of HE, several recommendations can be made. For treatment, rifaximin and lactulose combination therapy could be an option in patients with HE that is refractory to monotherapy. For the prevention of HE, rifaximin and lactulose combination therapy should be used in cases refractory to monotherapy, especially after the second episode of HE recurrence.

Summary

Evidence evaluating the use of combination therapy for the treatment of HE is limited and does not support its widespread use. All types of combination therapy should not be considered equivalent. Consideration may be given to the use of rifaximin and lactulose in the treatment of HE, especially in cases refractory to monotherapy. The combination of rifaximin and lactulose is recommended for the prevention of HE, especially after the second episode of HE recurrence.

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EXTRACTO

Terapia Combinada para el Tratamiento y Prevención de la Encefalopatía Hepática

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OBJETIVO: Evaluar la eficacia y seguridad de la terapia combinada para el tratamiento y prevención de la encefalopatía hepática (HE).

FUENTES DE DATOS: Se realizó una búsqueda en MEDLINE (1947-junio 2012) utilizando los términos lactulose, lactitol, non-absorbable disaccharide, metronidazole, rifaximin, neomicina, probiotics, y hepatic encephalopathy. Se limitaron las búsquedas a los artículos publicados en inglés.

SELECCIÓN DE ESTUDIOS Y EXTRACCIÓN DE DATOS: Se incluyeron ensayos clínicos, informes de casos, y series de casos de humanos con HE que fueron tratados con la terapia combinada de rifaximina, lactulosa, lactitol, metronidazol, neomicina, y/o probióticos.

SÍNTESIS DE DATOS: Hay pocos estudios que evalúen los beneficios de la terapia combinada. Analizamos seis estudios que evaluaban la terapia combinada en el tratamiento o la prevención de HE. Cuatro de ellos se

referían al tratamiento de la HE. Dos no encontraron diferencias entre lactulosa/neomicina y placebo o rifaximina/lactulosa. Un tercero analizaba rifaximina/lactulosa sin grupo control. El 4 no encontró diferencias entre lactulosa/probióticos y cualquiera de los 2 medicamentos administrados solos, aunque todos los grupos mostraron mejora del estado inicial. En los 2 ensayos sobre uso preventivo, ambos derivados de los mismos datos, la combinación rifaximina/lactulosa fue superior a lactulosa sola, mostrando mejoras significativas en el estatus mental, los niveles plasmáticos de amonio y la calidad de vida relacionada con la salud y reducciones en las recurrencias de HE y las hospitalizaciones. Actualmente no se dispone de estudios que evalúen la antibioterapia dual, la combinación de metronidazol con disacáridos no absorbibles, ni la de antibióticos con probióticos.

CONCLUSIONES: La evidencia disponible sobre el uso de terapia combinada en el tratamiento de HE no respalda su uso generalizado. La combinación de rifaximina y lactulosa puede ser considerada para el tratamiento de la HE, especialmente en pacientes refractarios a la monoterapia. Finalmente, la combinación de rifaximina y lactulosa debe ser tenida en cuenta para la prevención de la HE, especialmente tras el segundo episodio de recurrencia de la HE.

Traducido por Juan del Arco

RÉSUMÉ

Thérapie Combinée pour le Traitement et la Prévention de l'Encéphalopathie Hépatique

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OBJECTIF: Évaluer l'efficacité et l'innocuité de la thérapie combinée pour le traitement et la prévention de l'encéphalopathie hépatique (EH).

SOURCES DE DONNÉES: Une recherche PubMed a été effectuée (1947-juin 2012) en utilisant les mots clés lactulose, lactitol, non-absorbable disaccharide, metronidazole, rifaximin, neomycin, probiotics, et hepatic encephalopathy. Les recherches ont été limitées aux articles publiés en anglais.

SÉLECTION DES ÉTUDES ET EXTRACTION DES DONNÉES: La sélection des études incluait les essais cliniques publiés, les rapports de cas, et les séries de cas chez les humains qui ont été traités par une polythérapie incluant la rifaximine, lactulose, lactitol, métronidazole, néomycine, et/ou probiotiques.

SYNTHÈSE DES DONNÉES: Il y a peu d'études qui évaluent les avantages de la thérapie médicamenteuse combinée. Six études ont été identifiées pour le traitement ou la prévention de l'EH. Quatre études portaient sur le traitement de l'EH. Deux études n'ont trouvé aucune différence entre le lactulose/néomycine contre placebo ou rifaximine/lactulose. Une troisième étude a évalué la rifaximine/lactulose mais sans groupe-contrôle. La quatrième étude n'a trouvé aucune différence entre le lactulose/probiotiques par rapport au lactulose seul, bien que chaque groupe a montré une amélioration. Dans les 2 essais de prévention, la combinaison de la rifaximine/lactulose était supérieure au lactulose seul, démontrant une amélioration significative de l'état mental, des niveaux d'ammoniaque dans le sang, et des indicateurs de santé reliés à la qualité de vie et à la réduction des récurrences d'EH et d'hospitalisation. Aucune étude clinique n'a évalué une antibiothérapie double ou le métronidazole avec des disaccharides non absorbables ou des antibiotiques avec des probiotiques.

CONCLUSIONS: Les données évaluant l'utilisation de la thérapie combinée pour le traitement de l'EH ne supportent pas son utilisation à grande échelle. La combinaison de la rifaximine et du lactulose peut être considérée dans le traitement de l'EH et chez les patients réfractaires à la monothérapie. Enfin, la combinaison de la rifaximine et du lactulose devrait être envisagée pour la prévention de l'EH, surtout après le deuxième épisode d'EH.

Traduit par Nicolas Paquette-Lamontagne