Vol. 36 No. 4 - Apr. 2007

drug therapy topics

ISSN 0882-6684

Harborview Medical Center / Seattle Cancer Care Alliance / University of Washington Medical Center

Defending Champion *vs.* The New Kid On The Block:

Lactulose vs. Rifaximin for Acute Hepatic Encephalopathy

Helene Valderaz, Pharm.D.

Lactulose has been regarded as the gold standard treatment for acute hepatic encephalopathy since the 1980s.[1] However, inconvenient and undesirable gastrointestinal side effects are well documented with this agent.[2] Second-line treatment options include oral antibiotics such as neomycin, vancomycin, and metronidazole.[2] However, the potential for the development of systemic toxicity and concerns regarding microbial resistance limit the use of these agents. Rifaximin, an oral rifamycin antibiotic derivative, has recently come to the forefront of possible agents to consider when patients are intolerant or refractory to lactulose.[2] This article will briefly review the pathophysiology and current first-line therapy for acute hepatic encephalopathy, review why rifaximin is effective, and summarize data from head-to-head trials comparing rifaximin to lactulose so that practitioners will have a thorough understanding of how these two contenders compare.

Hepatic encephalopathy (HE), or portosystemic encephalopathy, is a neuropsychiatric syndrome that occurs in conjunction with acute or chronic hepatic disease. Portal-systemic shunting associated with hepatic dysfunction prevents the liver from sufficiently eliminating toxins, such as ammonia, from the systemic circulation and leads to HE. In turn, the resulting accumulation of ammonia in the central nervous system (CNS) leads to excitation of gamma-aminobutyric acid (GABA) receptors, thereby causing CNS depression.[3-5] This CNS depression is manifested by alterations in behavior and cognitive function (ranging from minimal disturbance to coma), sleep pattern disturbances, and muscular incoordination.[3-5] Other substances thought to be associated with the development of HE include manganese and endogenous benzodiazepines.[6,7]

The pathophysiology of HE is incompletely understood. However, predisposing factors that may precipitate HE are well established, and include metabolic abnormalities, medications, and increased ammonia production.[8,9] Metabolic abnormalities that may precede HE are alkalosis, hypoxemia, hyper- or hyponatremia, hypokalemia, etc. Medications associated with the development of HE include benzodiazepines, narcotic analgesics, sedatives, and diuretics.[5,8] Ammonia is naturally produced by aerobic and anaerobic bacteria as a by-product of the degradation of nitrogenous compounds in the colon.[6] Ammonia production may be increased as a result of excess dietary protein, constipation, uremia, and gastrointestinal bleeding.[5,8] Since liver function is compromised in HE and ammonia cannot be sufficiently eliminated, management is typically focused on supportive care and removal of identifiable precipitating factors, as well as minimizing the production and absorption of ammonia within the gastrointestinal tract.[5,10]

Current mainstay of pharmacologic treatment for HE includes the first-line use of non-absorbable disaccharides, such as lactulose.[1,2,4-7,11] Lactulose works via several mechanisms.[5,12] First, fermentation of lactulose by bacteria in the colon results in the production of organic acids that reduce colonic pH and inhibit urease-producing bacteria. Second, the decreased pH of the colon promotes production of ammonium ions, which are not readily

A University of Washington Drug Information Center publication
Distributed monthly by authority of the Pharmacy and Therapeutics Committee
Editor: Nelda A. Murri, Pharm.D. (206) 598-6612 – Asst. Editor: Elizabeth Rudy, D.V.M., R.Ph.
Department of Pharmacy Services / School of Pharmacy

Defending Champion *vs.* The New Kid On The Block (continued)

Lactitol is a non-absorbable disaccharide used in the treatment of HE. It is regulated in the US as a dietary supplement.

absorbed into the systemic circulation. Lastly, the cathartic effect of lactulose promotes the elimination of ammonia from the gut. A meta-analysis published in 2004 reviewed 22 clinical trials to assess the efficacy of non-absorbable disaccharides in HE.[1] Trials reviewed in the analysis included those comparing lactulose or lactitol to no intervention, placebo, or oral antibiotics. Of the 22 trials, only nine were classified as high-quality studies. While non-absorbable disaccharides tended to lower serum ammonia levels as expected, the overall improvement in HE was not shown to be statistically better than oral antibiotics.

While the overall clinical benefit is less clear, non-absorbable disaccharides effectively lower serum ammonia levels when used in HE.

Oral antibiotics that have been used for HE include neomycin, vancomycin, and metronidazole. Although oral vancomycin and neomycin are largely isolated to the gut, sufficient amounts may be systemically absorbed to expose patients to harmful side effects such as oto- and/or nephrotoxicity. In addition, neurotoxicity is a concern with metronidazole in this population. Thus, these agents have become less desirable options for HE. Rifaximin offers another option for the treatment of HE, with favorable tolerability and proven efficacy against common colonic bacteria.[5] Rifaximin is available on the UW Medicine formulary, with use restricted to Hepatology Service for patients that are HE intolerant or unresponsive to lactulose and/or neomycin.

Rifaximin has been licensed in Italy since 1987 and was granted orphan drug status for HE in the US in 1998. Rifaximin is currently FDA approved only for the treatment of travelers' diarrhea.

Rifaximin has been licensed in Italy for the treatment of gastrointestinal infections since 1987. In 1998 it was granted orphan status by the FDA for use in the treatment of HE. In 2001, Salix Pharmaceuticals, Inc. acquired the rights to license rifaximin in the US.[13,14] and in May 2004 it was approved by the FDA under the proprietary name Xifaxan^{R} for the treatment of travelers' diarrhea caused by *E. coli*. Like the structurally related drug, rifampin, rifaximin works by inhibiting bacterial RNA synthesis. It is beneficial in the treatment of HE due to minimal systemic absorption (<0.4%), broad-spectrum antimicrobial activity, and good patient tolerability.

There are approximately 22 clinical studies evaluating the use of rifaximin for the

Table II: Randomized Controlled Trials of Rifaximin *vs.* Lactulose
Part A - Study Characteristics

Study	N (men/women)	Population	Study Design	Study Duration	Treatment Arms and Doses
Fera, et al. 1993[17]	40 (29/11)	• Age 45-72 (mean 59) • All with cirrhosis and mild HE	Randomized, double-blind, double-dummy trial conducted in Italy	First 14 days of month for 3 months	Rifaximin 400mg Q 8h (n=20) vs. lactulose 27g Q 8h (n=20), administered for the first 14 days of each month
Massa, et al. 1993[18]	40 (27/13)	• Age 42-60 (mean 54.5) • All with cirrhosis and stage 2-3 HE (most stage 2)	Randomized, double-blind, double-dummy trial conducted in Itlay	15 days	7 day run-in period then: rifaximin 400mg Q 8h (n=20) vs. lactulose 20g Q 8h (n=20)
Paik, et al. 2005[19]	54 (37/17)	• Age 40-71 (mean 55.7) • All with cirrhosis (most with hepatitis B) and grade 1-3 HE	Randomized, unblinded study conducted in Korea	7 days	Rifaximin 1200mg/day in 3 divided doses (n=32) vs. lactulose 60g/day in 3 divided doses (n=22)

Defending Champion *vs.* The New Kid On The Block (continued)

Rifaximin is available on the UW Medicine formulary, with use restricted to Hepatology Service for patients that are HE intolerant or unresponsive to lactulose and/or neomycin.

The daily cost for therapy with rifaximin is 10x more than lactulose.

At least 22 clinical studies have evaluated the use of rifaximin for the treatment of HE. Five trials compared rifaximin to lactulose, but two of these employed suboptimal lactulose doses.[15,16] The quality of the three remaining studies[17-19] is debatable.

Table I: UW Medicine Formulary Drugs Used for Hepatic Encephalopathy

Drug	Antibacterial Activity	Daily Dose	Potential Adverse Effects	UWMC Inpatient Acquisition Cost per Day
Ampicillin	Broad spectrum	4g	Microbial resistance	$2.15
Lactulose	No direct activity	60-120g	Diarrhea, nausea, vomiting, flatulence, abdominal cramping	$2.00-3.80
Metronidazole	Anaerobic coverage	800mg	Neurotoxicity, disulfiram reaction with alcohol	$0.44
Neomycin	Aerobic coverage	4-6g	Nephro/ototoxicity	$13.00-20.00
Paromomycin	Broad spectrum	4g	Nephro/ototoxicity	$17.00
Rifaximin	Broad spectrum	1200mg	Headache	$22.00

treatment of HE. Of these, five are randomized controlled trials that specifically compared rifaximin to lactulose. Two of the five studies compared rifaximin to suboptimal doses of lactulose.[15,16] The remaining three studies are summarized in Table II. Two of these were randomized, double-blind, double-dummy studies, including 80 patients with HE and cirrhosis (40 patients treated with rifaximin).[17,18] The third study was a randomized, non-blinded study of 54 patients with HE and cirrhosis, predominantly in a subset of subjects with hepatitis B virus (32 patients treated with rifaximin).[19]

As is evident from the table, both rifaximin and lactulose are associated with a reduction in ammonia levels as well as improvement in HE severity, mental status, and other neurological signs and symptoms (asterixis, EEG abnormalities, A-cancellation test, and Reitan test). **Severity of HE** improved with both agents, with between-group differences

Table II: Part B - Study Outcomes

HE severity	Mental status	Ammonia	Asterixis	A-cancellation test	Reitan test	EEG
Decreased with both treatments, with statistically significant differences by day 15 favoring rifaximin ($p<0.05$)	• Progressive improvement with both treatments, but more consistent with rifaximin • No statistically significant difference seen within the first 2 weeks of treatment	• Reduction to normal levels seen with both therapies by day 10 • Statistical significance not reported	Statistically significant improvement by day 5 with both treatments	Similar trend toward improvement, but no difference between groups	Improvement with both treatments, but no statistically significant difference within the first 2 weeks of treatment	• Improvement with both groups, but trend toward faster improvement with rifaximin • Statistical significance seen after day 15 in favor of rifaximin ($p<0.01$)
• 14 cases regressed and 6 cases improved to stage 1 with rifaximin • 11 cases regressed, 2 cases improved to stage 2, and 7 cases improved to stage 1 with lactulose • No statistically significant difference, although 5 patients treated with rifaximin regressed completely after 8 days	• Progressive improvement with both treatments, with faster improvement with rifaximin • Statistically significant difference by day 15 in favor of rifaximin ($p<0.05$)	• Decreased to normal by day 6 with rifaximin and day 9 with lactulose • Statistically significant difference on day 15 ($p<0.05$)	• Progressive improvement with both treatments • Statistically significant difference only on day 6 ($p<0.05$), but similar scores at day 15	Similar trend in improvement with both treatments	• Improvement with both treatments • Statistically significant by day 15 in favor of rifaximin	• Normalized in 8 patients by day 6 with rifaximin vs. 4 patients by day 9 with lactulose • Statistically significant differences seen on day 6 and 9 favoring rifaximin ($p<0.01$ and $p<0.05$)
• Similar responses observed in ammonia level, mental status, asterixis, and Reitan test, but no statistically significant difference between treatments • Clinical efficacy (HE index improvemet) greater with lactulose (95.4% of patients) vs. rifaximin (84.4% of patients), though not statistically significant ($p=0.315$).						

HE severity or HE index is a composite of weighted parameters indicative of the signs and symptoms of HE (e.g., mental status, asterixis, EEG abnormalities, Reitan test, and ammonia level).

reported in one trial favoring rifaximin by day 15 of treatment.[17] **HE index** improvement with lactulose was reported to be 11% greater than rifaximin in one study, though this was not statistically significant.[19] There was a more consistent improvement in **mental status score** reported with rifaximin in two trials.[17,18] Mean mental status score improved from ~2 (semistupor and vague disorientation) to 1 (reduced attention span, vague drowsiness,and anxiety or euphoria) four days faster with rifaximin in one study[18] and in a second study, mental status scores for lethargy, constant disorientation, and inappropriate behavior improved from a score of 2.3 to 2 with lactulose, and to a score of 1 with rifaximin, by day 15 of therapy.[17] **Asterixis** significantly improved from baseline by day 5 with both rifaximin and lactulose in one of the three trials.[17] In one study the mean asterixis score improved from 2 (irregular occasional tremors) to 1 (rare tremors) after three days and after six days with rifaximin and lactulose, respectively; but, there was no difference in the time it took for asterixis to completely resolve.[18] **Ammonia levels** decreased to normal by day 10 of treatment with lactulose and rifaximin in one of the three studies,[17] and in a second study, ammonia levels normalized three days faster with rifaximin.[18]

In one comparative trial, HE index improved in 84% of patients given rifaximin and 95% of patients given lactulose, demonstrating similar efficacy between both treatments.[19]

Improvements in EEG abnormalities, the A-cancellation test, and the Reitan test were also seen with both rifaximin and lactulose. **EEG** normalization or significant improvement occurred three days sooner with rifaximin compared to lactulose in one trial.[18] **A-cancellation test** improvements were reported to be similar with both treatments in two studies.[17,18] Finally, **Reitan test** improvement was reported with both rifaximin and lactulose, with between-group differences noted by day 15 favoring rifaximin, in one study.[18] In each of the three trials, patients randomized to rifaximin tolerated the medication well, and those randomized to lactulose experienced gastrointestinal side effects early on in treatment.

A-cancellation test: An assessment of how many of 28 A's are crossed out in a grid of 100 letters.[17]

Reitan test: An assessment of the time needed to connect 25 progressive numbers.[17]

To summarize, these three head-to-head trials clearly illustrate the comparable efficacy of rifaximin and lactulose in the treatment of HE. Statistically significant differences between treatment groups in neurological signs and symptoms in some trials tended to favor rifaximin (i.e., mental status, EEG abnormalities, and ammonia levels), but these differences were not consistent from trial to trial. Overall, rifaximin appears to decrease ammonia levels and improve asterixis as quickly as lactulose, with trends toward faster improvement in HE severity, mental status, EEG abnormalities, and A-cancellation and Reitan neurological tests. No information on overall clinical outcomes was provided by these studies, thus it is unclear if the trends toward faster improvements with rifaximin translate into more favorable outcomes (such as sooner discharge from the hospital) compared to lactulose. Additionally, the scoring of improvements across studies is variable, making the comparative magnitude of overall effects difficult to discern for either agent. Given this and the small size of these studies (a total of 72 patients treated with rifaximin), it is difficult to conclude that rifaximin should be used first-line over lactulose. Also of note, though not mentioned as a possible concern in the comparative trials, is the potential for the development of microbial resistance if rifaximin were to replace lactulose as first-line therapy for HE.

As evaluated in existing published clinical trials of HE, the ultimate clinical gain that results from improving EEG abnormalities and certain other measurable neurological parameters (e.g., asterixis) with either rifaximin or lactulose remains unproven.

Despite the cost difference of rifaximin compared to lactulose (see Table I), a question arises as to whether it is reasonable to postulate that faster trends toward improvement in parameters such as mental status, HE severity, and ammonia levels with rifaximin in the acute-care setting could facilitate faster patient discharges from the hospital and lower overall healthcare costs. Regrettably, however, the two published retrospective studies of cost examined HE-related hospitalizations during rifaximin or lactulose *maintenance* therapy.[20,21] Neff et al.[20] reported three HE-related hospitalizations with rifaximin (n=15) vs. 19 with lactulose (n=24), an average length of stay of 3.5 days with rifaximin vs. 5 days with lactulose, and an average annual cost difference of therapy per patient of $5,300 favoring rifaximin. Leevy et al.[21] (n=145 treated with lactulose then rifaximin) reported

Exploiting two different mechanisms of action to treat HE may be beneficial; however, rifaximin + lactulose combined has never been compared to monotherapy with either agent alone. If the two are used together, consider separating their administration by at least 2 hours in order to maximize rifaximin retention in the colon.

Flumazenil (a benzodiazepine receptor antagonist) has been postulated as a possible treatment for HE.[6,7,22]

Lactulose should retain its title as first-line therapy for HE, with rifaximin best reserved as a second-line agent for patients who are unable to tolerate side effects or who are refractory to lactulose.

Note: The editor and author gratefully acknowledge the assistance of Thomas H. Payne, M.D., Marcela M. Aguilar, Pharm.D., and Shay Keen, Pharm.D. in reviewing this article.

0.5 hospitalizations during treatment with rifaximin vs. 1.6 during treatment with lactulose, 2.5 days of hospitalization with rifaximin vs. 7.3 with lactulose, and a difference in hospitalization charges per patient of $42,400 favoring rifaximin. Unfortunately, these data lack applicability to the acute-care setting and both analyses were limited by a retrospective study design, small N, and patient self-reports of adherence to therapy.

Treatment of HE is challenging. It is a multifactorial disease and the pathogenesis is incompletely understood. Prescribers face difficulties in treating this population in particular, as many patients may be noncompliant secondary to intolerable side effects of lactulose, or may suffer from disease that is not responsive to lactulose. Comparative trials of rifaximin vs. lactulose have consistently shown rifaximin to be as beneficial as lactulose in the treatment of HE. While trends toward statistical significance and faster resolution of signs and symptoms are noted with rifaximin in these trials, there is no evidence that these trends positively effect overall clinical outcomes or cost. Thus, because of the cost difference and potential for emergence of microbial resistance, lactulose should retain its title as "first-line therapy for HE," with rifaximin best reserved as a second-line agent for patients who are unable to tolerate, or who are refractory to, lactulose.

References:

1. Als-Neilsen B, Gluud L, Gluud C. Non-absorbable disaccharides for hepatic encephalopathy: systematic review of randomised trials. BMJ 2004; 328: 1046-51.
2. Blei A, Cordoba J, Gastroenterology TPPCotACo. Practice guidelines: hepatic encephalopathy. Am J Gastroenterol 2001; 96(7): 1968-76.
3. Ferenci P. Clinical manifestations and diagnosis of hepatic encephalopathy: In: UpToDate online version 15.1. (C)2007. UpToDate, Waltham, MA. Available at: www.uptodate.com [Last accessed 03/05/07].
4. Zeneroli M, Avallone R, Corsi L,et al. Management of hepatic encephalopathy: role of rifaximin. Chemotherapy 2005; 51(Supp1): 90-5.
5. Festi D, Vestito A, Mazzela G, et al. Management of hepatic encephalopathy: focus on antibiotic therapy. Digestion 2006; 73(Supp1): 94-101.
6. Mas A. Hepatic encephalopathy: from pathophysiology to treatment. Digestion 2006; 73(Supp 1): 86-93.
7. Bass N. Review article: the current pharmacological therapies for hepatic encephalopathy. Aliment Pharmacol Ther 2006; 25(Supp 1): 23-31.
8. Ferenci P. Pathogenesis of hepatic encephalopathy. In: UpToDate online version 15.1. (C) 2007. UpToDate, Waltham, MA. Available at: www.uptodate.com [Last accessed 03/05/07].
9. Sanaka M, Ong J, Mullen K. Challenges of designing hepatic encephalopathy treatment trials. Hepatology 2003; 38: 527-9.
10. Mas A, Rodes J, Sunyer L, et al. Comparison of rifaximin and lactitol in the treatment of acute hepatic encephalopathy: results of a randomized, double-blind, double-dummy, controlled clinical trial. J Hepatol 2003; 38: 51-8.
11. Ferenci P, Lockwood A, Mullen K, et al. Hepatic encephalopathy - definition, nomenclature, diagnosis, and quantification: final report of the Working Party at the 11th World Congress of Gastroenterology, Vienna, 1998. Hepatology 2002; 35: 716-21.
12. Timm E, Stragand J. Portal hypertension and cirrhosis. In: Dipiro J, Talbert R, Yee G, et al., (eds). Pharmacotherapy: a physiologic approach. 5th ed. New York: McGraw-Hill; 2002: 671-91.
13. Cumulative list of all orphan designated products. U. S. Food and Drug Administration, Office of Orphan Products Development. Rockville, MD. www.fda.gov/orphan/designat/alldes.rtf [Last accessed 03/17/07].
14. Center for Drug Evaluation and Research. Application number 21-361. AdXifaxan (administration document(s) part 1). www.fda.gov/cder/foi/nda/2004/21-361_Xifaxan_Admindocs_P1.pdf [Last accessed 03/17/07].
15. Bucci L, Palmieri G. Double-blind, double-dummy comparison between treatment with rifaximin and lactulose in patients with medium to severe degree hepatic

Pharmacy & Therapeutics Committee Actions

Formulary Additions	Dosage Form	Classification	Use	Usual Dose
Varenicline (Chantix)	Tablet: 0.5mg,1mg	Smoking deterrent	Aid to smoking cessation treatment	1mg BID, following a 1-week titration
Other Actions				
UWMC Pharmacy Pre-Pack Discharge Prescription Policy	To expedite the process of discharging patients from the hospital, UWMC pharmacy was granted authorization to dispense oxycodone 5mg, acetaminophen 325mg-oxycodone 5mg, and docusate sodium 250mg in standardized pre-count multiples of #20 and #30. **<UWMC Pre-Pack Discharge Dispensing Policy>** The quantity dispensed for a schedule II narcotic will be decreased to the nearest pre-pack quantity for oxycodone 5mg and oxycodone 5mg-acetaminophen 325mg prescriptions for UWMC, Roosevelt, and Pavilion discharge patients. The maximum reduction in quantity will be by nine tablets. For example, a prescription written for oxycodone 5mg #24 will be reduced to #20 tablets. If the prescriber writes for a specific days' supply on the prescription, the quantity will be dispensed as written.			

Defending Champion *vs.* The New Kid On The Block (continued)

encephalopathy. Curr Med Res Opin 1993; 13(2): 109-18.

16. Festi D, Mazzela G, Orsini M, et al. Rifaximin in the treatment of chronic hepatic encephalopathy: results of a multicenter study of efficacy and safety. Curr Ther Res 1993; 54(5): 598-609.
17. Fera G, Agostinacchio F, Nigro M, et al. Rifaximin in the treatment of hepatic encephalopathy. Eur J Clin Res 1993; 4: 57-66.
18. Massa P, Vallerino E, Dodero M. Treatment of hepatic encephalopathy with rifaximin: double blind, double dummy study versus lactulose. Eur J Clin Res 1993; 4: 7-18.
19. Paik Y, Lee K, Han K, et al. Comparison of rifaximin and lactulose for the treatment of hepatic encephalopathy: a prospective randomized study. Yonsei Med J 2005; 46(3): 399-407.
20. Neff G, Kemmer N, Zacharias V, et al. Analysis of hospitalizations comparing rifaximin versus lactulose in the management of hepatic encephalopathy. Transplant Proc 2006; 38: 3552-5.
21. Leevy C, Phillips J. Hospitalizations during the use of rifaximin versus lactulose for the treatment of hepatic encephalopathy. Dig Dis Sci 2007; 52: 737-41.
22. Heidelbaug J, Sherbondy M. Cirrhois and chronic liver failure: part II, complications and treatment. Am Fam Physician 2006; 74:767-76.

Vol. 36, No. 4

UNIVERSITY OF WASHINGTON

DRUG INFORMATION CENTER
Box 354735
Seattle, WA 98195-4735

drug therapy topics