

Rifaximin Tablets

(Xifaxan® - Salix Pharmaceuticals)

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Rifaximin is a broad-spectrum antibiotic, a derivative of rifamycin with very low gastrointestinal absorption. As such, its utility is limited to treatment of conditions occurring within the GI tract. It is FDA-approved for the treatment of traveler's diarrhea, but has a significant amount of off-label use in hepatic encephalopathy and is being studied for other indications including inflammatory bowel disease, pouchitis and *Clostridium difficile* colitis.

PHARMACOLOGY

Rifaximin was developed as a semi-synthetic derivative of rifamycin with the intent to create a compound with minimal systemic absorption and with broad-spectrum antibacterial activity.¹ It has inhibitory activity against gram-positive, gram-negative and anaerobic organisms, including many GI pathogens. Rifaximin's antimicrobial activity occurs through the drug's binding of the β -subunit of bacterial DNA-dependent RNA polymerase and displacing catalytic magnesium ions, inhibiting bacterial RNA synthesis.

PHARMACOKINETICS

Following oral administration, nearly 97% of a dose is excreted unchanged in the feces.² Less than 1% is excreted in the urine. The C_{max} averages 4.3 ± 2.8 ng/mL with an AUC of 19.5 ± 16.5 ng·h/mL and a half-life of 1.25 hours. Drug concentrations in the feces on the day following a three-day regimen of rifaximin 400 mg PO every 12 hours averaged 7961 mcg/g and dropped off gradually over the next five days.³ No pharmacokinetic studies have been performed in patients older than 65 years, younger than 18 years or with renal insufficiency, nor have gender differences in rifaximin pharmacokinetics been studied.¹ In patients with hepatic insufficiency, no pharmacokinetic differences have been observed and no dosing adjustments are necessary in these patients.

MICROBIOLOGY/RESISTANCE

Gomi et al. tested the activity of eleven different antimicrobials including rifaximin against bacterial pathogens obtained from the stools of adults with travelers' diarrhea.⁴ Isolates were obtained from patients in India, Jamaica, Mexico and Kenya. The MIC₉₀ for rifaximin against enterotoxigenic *Escherichia coli* (ETEC), enteroaggregative *E. coli* (EAEC), *Salmonella* species, *Shigella* species and *Campylobacter* species ranged from 32 mcg/mL to 64 mcg/mL, rather high values but well below the con-

Summary

Indications. Rifaximin is indicated for the treatment of travelers' diarrhea caused by noninvasive strains of *Escherichia coli* in patients 12 years old and older.

Monitoring parameters. Patients should be monitored for the resolution of the signs and symptoms of travelers' diarrhea, including passing unformed stools, abdominal cramping, fever and fecal urgency. Patients should also be monitored for the development of rash, urticaria and pruritus; muscle spasms, myalgia and arthralgia; abnormal blood counts, elevated liver function tests and hematuria.

Dose. The recommended dose for travelers' diarrhea is 200 mg three times daily for three days. Rifaximin may be taken without regard to food.

Pediatrics. The safety and efficacy of rifaximin in patients under 12 years old have not been evaluated.

Geriatrics. No data on differences in pharmacokinetics in the elderly.

Race. No data on differences in pharmacokinetics due to race.

Renal insufficiency. No data on differences in pharmacokinetics due to renal insufficiency.

Hepatic insufficiency. Due to minimal systemic bioavailability, no dose adjustments are necessary in hepatic insufficiency.

Pregnancy category. C

Breastfeeding. No data on breast milk excretion.

Cost. The Average Wholesale Price of rifaximin is \$4.13 for a 200-mg oral tablet. The cost for a three-day course for the treatment of travelers' diarrhea would be \$37.17.

 ARCHIVES OF PHARMACOTHERAPY PERSPECTIVES
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centration of rifaximin present in fecal material after three days of treatment.^{3,4}

Sierra et al. tested the activity of rifaximin and other common antimicrobials against stock cultures of bacteria commonly found to cause travelers' diarrhea.⁵ The MIC₉₀ values for most organisms ranged from 4 to 16 mcg/mL, with *Campylobacter jejuni* and *Yersinia enterocolitica* as exceptions with MIC₉₀ values of 512 mcg/mL and 128 mcg/mL, respectively.

Hoover et al. determined the activity of rifaximin against gram-positive and gram-negative organisms from stock cultures.⁶ Rifaximin was highly active against *Staphylococcus* species, *Streptococcus* species, *Enterococcus* species and anaerobes, but was less active against gram-negative organisms, including *Salmonella* species, *Shigella* species and *Citrobacter* species.

The *in vitro* and *in vivo* activities of rifaximin were evaluated by Venturini and Marchi.⁷ Rifaximin was as effective as rifampin and superior to neomycin against *Staphylococcus aureus* isolates. Gram-negative organisms, including *E. coli*, *Salmonella* spp., *Serratia* spp and others, were as susceptible to rifaximin as to rifampin and neomycin. The MICs of *Salmonella* spp., *Proteus mirabilis*, *Serratia* spp. and *E. coli* isolates increased with increasing inoculum size.

Lamanna and Orsi compared the activity of rifaximin to that of rifampin against 92 clinical isolates of *Bacteroides* species and 15 clinical isolates of *Clostridium perfringens*.⁹ Rifaximin was comparable to rifampin in activity and inhibited 72% of *Bacteroides fragilis* strains at concentrations ≤ 4 mcg/mL; 100% of other *Bacteroides* species and 100% of *C. perfringens* isolates were inhibited at those concentrations.

CLINICAL TRIALS

Travelers' Diarrhea

Rifaximin has been evaluated in the treatment of travelers' diarrhea in adults and children in four randomized, double blind trials.¹⁰⁻¹³ In all studies, travelers' diarrhea was defined as having three or more unformed stools in the 24 hours prior to enrollment plus one or more signs or symptoms of enteric infection. The primary endpoint in the trials was the time to last unformed stool (TLUS); secondary endpoints included the number of patients showing improvement, number of unformed stools per 24-hour period, number of treatment failures, clinical cure rates and microbiological cure rates.

In a placebo-controlled trial that included 349 evaluable subjects with travelers' diarrhea in Mexico, Guatemala and Kenya, the TLUS was significantly shorter among patients taking rifaximin 200 mg three times daily (32.5 hrs) or 400 mg three times daily (32.9 hrs) than among patients taking placebo (60.0 hrs; $p=0.0001$ for both rifaximin groups vs. placebo).¹⁰ The treatment period was three days. Patients taking a higher dose of rifaximin, 400 mg three times daily, did not show significantly higher efficacy except among patients with leukocyte-positive stools; the higher dose was associated with more frequent side effects, such as headache (15.1%) and fatigue (1.1%). Both rifaximin doses were associated with significantly higher rates of clinical cure (79.2% and 81.0% [rifaximin 600 mg/day, 1200 mg/day, respectively] vs. 60.5% for placebo; $p=0.001$) and fewer treatment failures (16.0% and 16.7% vs. 34.9%; $p=0.001$). Microbiological cure rates did not differ among the study groups.

A study of patients with travelers' diarrhea in Mexico, Guatemala, India and Peru compared rifaximin 200 mg three times daily ($n=197$) to placebo ($n=101$) and ciprofloxacin 500 mg twice daily plus placebo once daily ($n=101$) for three days.¹¹ Patients taking rifaximin had more rapid improvement of median TLUS (32.0 hrs) compared to placebo (65.5 hrs, $p=0.0014$), but not compared to ciprofloxacin (median TLUS = 28.8 hrs;

p not stated). Clinical cure rates were higher for both rifaximin (76.6%) and ciprofloxacin (78.2%) than for placebo (61.4%) ($p=0.0039$ vs rifaximin and $p=0.007$ vs. ciprofloxacin). Adverse events occurred in 14.0% of the ciprofloxacin-treated patients, 10.6% of the rifaximin-treated patients and 10.0% of the placebo-treated patients. Headache (7.5%) and constipation (5.3%) were reported most frequently.

Three doses of rifaximin were compared to TMP/SMX in the treatment of travelers' diarrhea in Mexico.¹² The TLUS was not significantly different among patients taking either 200 mg ($n=18$; 36.9 hrs), 400 mg ($n=18$; 38.6 hrs), or 600 mg ($n=19$; 53.0 hrs) of rifaximin three times daily (overall average=43.1 hrs) compared to that of 17 patients receiving TMP/SMX 160/800 mg twice daily for 5 days (55.7 hrs). The groups did not differ significantly in clinical cure rates, microbiological cure rates or failure rates. No drug-related adverse effects were noted in any arm of the study.

A fourth trial compared rifaximin 400 mg twice daily ($n=93$) to ciprofloxacin 500 mg twice daily ($n=94$) for three days.¹³ Subjects were visitors to Mexico and Jamaica with travelers' diarrhea. There were no significant differences between rifaximin and ciprofloxacin in TLUS (25.5 hrs vs 25.0 hrs, respectively; $p=0.614$), clinical cure rates (87% vs. 88%; $p=0.803$) or treatment failures (10% vs. 6%; $p=0.258$). Microbiologic failures were more frequent with rifaximin than with ciprofloxacin among patients who had enterotoxigenic *E. coli* as the sole pathogen (RR=2.42; 95% CI 0.85-6.5). Adverse effect reporting was similar for both groups, with dizziness, headache, fatigue, constipation and cough being cited frequently.

Rifaximin is also effective for prevention of travelers' diarrhea in adults.¹⁴ A study of 200 American students visiting Mexico compared rifaximin 200 mg once, twice or three times daily to placebo for two weeks in the prevention of diarrhea, defined as passing ≥ 3 unformed stools every 24 hours plus one sign or symptom of enteric infection. The rate of prevention of diarrhea over the two-week treatment period was 72% ($p=0.0001$), with 31% and 32% of patients in the placebo group developing diarrhea in weeks one and two, respectively, compared to 2% and 10%, 13% and 7%, and 4% and 10% of patients taking rifaximin one, two and three times daily, respectively. No differences between the groups were found in the number of coliform organisms isolated from stool samples collected during the treatment period.

Hepatic Encephalopathy

Rifaximin has been compared to lactulose, the current standard of therapy, in patients with hepatic encephalopathy. Bucci and Palmieri conducted a randomized, double-blind, double-dummy trial in 58 patients with moderate to severe hepatic encephalopathy.¹⁵ Patients were randomized to receive rifaximin 400 mg plus a 10 g placebo packet or placebo tablets plus a 10 g packet of lactulose three times daily for 15 days. Patients were evaluated at entry and every three days thereafter for mental status, using the Parson-Smith semi-quantitative scale; asterixis; cancellation test; trail-making test and electroencephalogram. Each parameter was scored on a 0 to 4 scale. Fasting serum ammonia concentrations were also monitored. The degree of severity of encephalopathy

was also evaluated using a 0 to 20 scale in which state of consciousness, intellectual functions, behavior and neurological symptoms were assessed.

Patients' mental state as measured on the Parson-Smith scale improved with both treatments; statistically significant improvement occurred in the rifaximin group on day 6 and in the lactulose group on day 12. By day 9, the improvement in the rifaximin group was significantly superior to that of the lactulose group ($p < 0.01$). There was no difference between the treatments in the degree of improvement in asterixis, the cancellation test or the trail-making test. Improvements in EEG irregularities showed improvement in the rifaximin group by day 6 and in the lactulose group by day 9, and the rifaximin group had significantly greater improvement on days 6, 12 ($p < 0.05$ for both) and 15 ($p < 0.01$). Fasting serum ammonia concentrations decreased in both groups, with statistically significant improvement over baseline values seen at day 3 in both. The rifaximin group had significantly greater improvement on days 3, 5 and 12. Degree of severity scores improved in both groups, but statistically significant improvement was not seen until day 12 in either group; on day 12, the rifaximin group was significantly more improved than the lactulose group.

Adverse effects were for the most part mild, with 6.7% of patients in the rifaximin arm reporting abdominal pain, 16.7% reporting flatulence and 6.7% reporting weight loss. Diarrhea, dyspepsia, anorexia and flatulence were reported in half or more of the patients receiving lactulose. No patients withdrew from the study because of adverse effects. The authors concluded that rifaximin was suitable for the treatment of hepatic encephalopathy and was better tolerated than lactulose. However, the placebo powder used in the rifaximin arm was sorbitol which, like lactulose, is a hyperosmotic laxative that also reduces the pH of fecal matter; therefore, it is difficult to attribute the modest superiority of rifaximin in this study to rifaximin alone.

Paik et al. compared rifaximin to lactulose in a randomized, open-label study.¹⁶ Fifty-four patients with mild to moderate hepatic encephalopathy as measured by the Parson-Smith criteria were randomized to receive rifaximin 400 mg three times daily or lactulose syrup 90 mL daily for seven days. Patients were evaluated before treatment and on days 3, 5 and 7 for Parson-Smith scale score, asterixis, number connection test and blood ammonia concentrations, with each test graded on a 0 to 4 scale. The mental status score was weighted by a factor of three in calculating an overall portosystemic encephalopathy (PSE) score. Statistically significant improvements in each parameter were observed by the end of the treatment period in both treatment groups. There was no difference between the groups in the degree of improvement of any parameter at any time during the study. There was no difference in the rate of efficacy between the two groups. Adverse effects were infrequent; one patient in the rifaximin group reported abdominal pain and one patient in the lactulose group had severe diarrhea. No patient withdrew from the study due to adverse effects.

Rifaximin was compared to lactitol in 103 patients enrolled in a randomized, double-blind, double-dummy clinical trial.¹⁷ Eligible patients were those diagnosed with cirrhosis who had grade I-III hepatic encephalopathy for two days or less. A sub-

optimal randomization procedure was used for assignment of patients. Patients received rifaximin 400 mg plus 20 g of placebo powder (composition unspecified) or placebo tablets plus 20 g lactitol powder three times daily for five days; the treatment could be continued for five more days if the encephalopathy had not resolved. Efficacy was measured by changes in PSE index in terms of mental status (weighted by a factor of three), asterixis, the number connection test (NCT), EEG abnormalities and serum ammonia concentrations. The two groups were similar in demographic and clinical parameters with the exception of height ($p = 0.024$ for lactitol greater than rifaximin), the presence of ascites ($p = 0.0483$ for lactitol greater than rifaximin) and in the mean stage of encephalopathy as determined by the number connection test ($p = 0.0391$ for lactitol greater than rifaximin).

Statistically significant improvements were observed in both treatment groups on all measures at the end of the treatment period. There were no significant differences between the groups except in serum ammonia concentrations ($p = 0.008$ for rifaximin superior to lactitol), mean PSE index ($p = 0.0103$ for rifaximin superior to lactitol) and mean improvement rate in hepatic encephalopathy clinical syndrome ($p = 0.0083$ for rifaximin superior to lactitol when NCT is included; $p = 0.0153$ for rifaximin superior to lactitol when NCT is not included). Side effects in both groups were generally mild and included abdominal pain, mild diarrhea and vomiting; no severe adverse effects were attributed to the study drugs. The authors concluded that rifaximin was equivalent to lactitol from a clinical standpoint in the treatment of hepatic encephalopathy.

Rifaximin was shown to be effective in improving PSE index scores in 26 patients who could not tolerate or were unresponsive to treatment with lactulose in an uncontrolled, open-label study.¹⁸ Seventeen patients were classified as intolerant to lactulose because they developed intolerable side effects on therapeutic doses of lactulose (approximately 50 g/day), and nine patients were classified as nonresponders because they had no improvement in hepatic encephalopathy grade or blood ammonia concentrations after 15-30 days of treatment with therapeutic doses of lactulose. Treatment with 400 mg rifaximin three times daily for ten days was initiated after a two to three week washout period. The PSE index and laboratory data were measured at baseline and at the end of therapy. Compliance was assessed by a count of remaining tablets after the treatment period.

After ten days of therapy, there were significant improvements over baseline in the mental state ($p < 0.05$), asterixis ($p < 0.05$) and ammonia concentration ($p < 0.001$) among patients intolerant to lactulose, and significant improvements in mental state ($p < 0.05$) and number-connection test scores ($p < 0.05$) among nonresponders. No significant differences between the two groups were noted for any parameter in the PSE index. Overall improvement in the PSE index compared to baseline was significant for both intolerants ($p < 0.01$) and nonresponders ($p < 0.05$). Laboratory tests found a significant increase in WBC ($p < 0.01$) and a significant decrease in serum creatinine ($p < 0.05$) relative to baseline among nonresponders at the end of therapy.

Compliance was very good (0 unused tablets) in 2 (7.7%) patients, good (1 to <10 unused tablets) in 22 (84.6%) of patients and moderate (10-20 unused tablets) in 2 (7.7%) patients. There

TABLE 1. IN VITRO ACTIVITY OF RIFAXIMIN: GRAM-NEGATIVE BACTERIA

Organism	Number of isolates	MIC50 (mcg/mL)	MIC90 (mcg/mL)	Ref.
ETEC*	97		32	4
ETEC	38	8	16	5
EAEC**	75		32	4
EAEC	28	8	16	5
<i>E. coli</i>	20	8	>8	6
<i>E. coli</i>	15	6.25	25	7
<i>Salmonella enteritidis</i>	10	2	8	6
<i>Salmonella</i> spp.	46		64	4
<i>Salmonella</i> spp.	14	4	4	5
<i>Salmonella</i> spp.	56	6.25	12.5	7
<i>Shigella</i> spp.	36		64	4
<i>Shigella</i> spp.	10	4	8	6
<i>Shigella flexneri</i>	28	4	16	5
<i>Shigella sonnei</i>	36	8	16	5
<i>Aeromonas hydrophila</i>	11	8	8	5
<i>C. jejuni</i>	12	256	512	5
<i>C. jejuni</i>	54	12.5	100	8
<i>Y. enterocolitica</i>	10	64	128	5
<i>Y. enterocolitica</i>	10	8	>8	6
<i>Y. enterocolitica</i>	74	6.25	12.5	8
<i>Serratia</i> spp.	10	50	>50	7
<i>Enterobacter</i> spp.	50	≥4	≥8	6
<i>Enterobacter</i> spp.	6		25	7
<i>Citrobacter</i> spp.	30	>8	>8	6
<i>Citrobacter</i> spp.	4		>25	7
<i>Klebsiella</i> spp.	30	>8	>8	6
<i>Proteus</i> spp.	30	≥4	≥4	6
<i>Proteus</i> spp.	26	25	50	7
<i>Acinetobacter</i> spp.	10	2	4	6
Other‡	21		4	4

*ETEC – Enterotoxigenic *E. coli*
 **EAEC – Enteroaggregative *E. coli*
 ‡Other – *Vibrio* spp. other than cholera-causing species; *Plesiomonas shigelloides*; *Aeromonas* spp.

were no significant adverse effects reported during the study period. The authors concluded that rifaximin could be considered as add-on or alternative treatment in hepatic encephalopathy.

Festi et al. evaluated the efficacy and safety of rifaximin in 136 patients with mild hepatic encephalopathy.¹⁹ Eighty patients received rifaximin 1200 mg/day in an open-label trial; 35 patients were randomized to receive rifaximin 1200 mg/day (n=20) or neomycin 3000 mg/day (n=15); and 21 patients were randomized to receive rifaximin 1200 mg/day (n=9) or lactulose 40 g/day (n=12). These study protocols contained no blinding procedures. The duration of treatment in all study arms was 21 days. Neurologic signs and symptoms as well as blood ammonia con-

TABLE 2. IN VITRO ACTIVITY OF RIFAXIMIN: GRAM-POSITIVE BACTERIA

Organism	Number of isolates	MIC50 (mcg/mL)	MIC90 (mcg/mL)	Ref.
<i>Staphylococcus aureus</i> (OSSA*)	40	0.015	≤0.015	6
<i>S. aureus</i> (ORSA**)	11	≤0.015	>8	6
<i>S. aureus</i>	30	0.045	1.5	7
<i>Staphylococcus epidermidis</i>	20	≤0.015	≤0.015	6
<i>Streptococcus</i> spp.	84	≤0.12	≤0.25	6
<i>Enterococcus faecalis</i>	21	2	8	6
<i>Enterococcus faecium</i>	11	2	>8	6
<i>Enterococcus</i> spp.	10	0.25	2	6
<i>C. difficile</i>	56	0.39	100	8

*OSSA – Oxacillin-sensitive *S. aureus*
 **ORSA – Oxacillin-resistant *S. aureus*

centrations were measured at baseline and every two days during the studies; laboratory tests were performed at baseline and at the end of the study.

In the study of rifaximin alone, significant reductions (p<0.05) in the frequency of asterixis and in blood ammonia concentrations were seen by the fifth day of treatment and for the remainder of the study period. Asterixis was eliminated in all patients after 15 days of treatment. The frequency of EEG abnormalities was significantly reduced (p<0.01) after five days of treatment. Blood ammonia decreased significantly (p<0.01) from baseline on the fifth day of treatment. In addition, mean serum bilirubin was significantly decreased (p<0.05) at the end of the study period. No other significant differences in laboratory tests were noted and no significant side effects were reported.

In the rifaximin vs. neomycin portion of the study, both drugs effectively reduced the frequency of asterixis and EEG abnormalities; significant improvement over baseline was noted on day 3 in the rifaximin group and day 5 in the neomycin group. The authors did not indicate whether the difference between the two groups in response time was significantly different. In the rifaximin group, statistically significant increases over baseline in mean serum sodium and in mean serum albumin were noted (p<0.05 for both). No other significant differences in laboratory values occurred. The authors reported that rifaximin and neomycin were well tolerated.

In the rifaximin vs. lactulose portion of the study, significant reductions (p<0.01) in the frequency of asterixis and EEG abnormalities as well as in blood ammonia levels were seen by day 3 in both treatment groups. A significant increase (p<0.05) from baseline in mean serum sodium concentration was observed in the rifaximin group; no other significant changes in laboratory values occurred. In the lactulose group, nausea and abdominal cramps were reported early in the treatment period but these symptoms resolved during the course of therapy. Rifaximin was well tolerated. The authors concluded that rifaximin was safe and effective in reducing the signs of hepatic encephalopathy and that it was at least comparable to neomycin and lactulose, per-

haps producing a faster response than the comparator drugs.

Rifaximin was compared to neomycin for hepatic encephalopathy in two randomized trials and one double cross-over trial in 104 patients.²⁰⁻²² In the first study, patients were randomized to receive 400 mg rifaximin (n=30) or 1 g neomycin (n=30) three times daily for 14 consecutive days each month for 6 months.²⁰ Both groups had significant improvement ($p<0.001$) in the signs and symptoms of hepatic encephalopathy, including speech disturbances, memory, behavior and mood, gait, asterixis, serial number subtraction and drawing a five-pointed star, within 30 days of beginning treatment. Blood ammonia concentrations were significantly decreased ($p<0.001$) by the end of the trial. No significant differences were noted between the two groups except in the number-connection test, where the rifaximin group improved significantly ($p<0.02$) and the neomycin group did not improve. Two patients in each arm dropped out of the study due to nausea or dyspepsia and two more in the neomycin arm dropped out due to diarrhea. Five patients were lost to follow-up.

In the second trial, patients (n=14) received 400 mg rifaximin or 1.5 g neomycin three times daily for seven days, followed by a weeklong washout period after which they received the alternate treatment.²¹ Lactulose 10-60 g/day was also administered throughout the trial and washout periods. Neither treatment significantly improved the signs and symptoms of hepatic encephalopathy. There were no significant differences between the groups.

The third study, a double-blind, randomized trial, compared rifaximin 400 mg three times daily (n=15) to neomycin 1 g three times daily (n=15) in decreasing blood ammonia in patients with hepatic encephalopathy.²² Blood ammonia concentrations were measured at baseline and on treatment days 3, 7, 14 and 21. Mental state and psychometric performance were also monitored throughout the trial. Both treatments produced statistically significant improvements in blood ammonia, EEG abnormalities, the number-connection test and frequency of asterixis. Patients in the rifaximin group had a significantly greater ($p<0.005$) reduction in blood ammonia on days 14 and 21, but there were no differences between the groups in the other measures. No adverse effects were reported in the rifaximin group, while mild adverse effects including nausea, abdominal pain, vomiting and increases in BUN and creatinine, were reported in the neomycin group.

Williams et al. conducted a randomized, double-blind trial to determine the safety and efficacy of three doses of rifaximin in 54 patients with hepatic encephalopathy.²³ Patients with mild to moderate hepatic encephalopathy were randomized to receive 600, 1200 or 2400 mg rifaximin in three divided doses daily for seven days. PSE index (measured on a 0-100% scale), blood ammonia concentrations, serum chemistry and hematology were evaluated before and after the treatment period. Patients in all three groups had improvement in the PSE index by the end of treatment, although statistically significant changes in the index were seen only in the groups dosed at 1200 mg (95% CI -17.4 to -3.1) and 2400 mg (95% CI -17.8 to -3.6). Significant differences between the groups were not observed. Blood ammonia did not decrease significantly in any group. Adverse events attributed to the study drug were infrequent and included one case of ascites, two cases of candidiasis and two cases of nausea; both

cases of nausea were in the 2400 mg/day group). There were no withdrawals from the study due to adverse effects. No abnormalities in laboratory tests were attributed to rifaximin. The authors concluded that rifaximin 1200 mg/day may be considered for add-on or alternative therapy for hepatic encephalopathy in patients who do not tolerate or do not respond to lactulose or lactitol.

Other gastrointestinal disorders

Rifaximin has been studied as adjuvant therapy in a small pilot study in ulcerative colitis (UC).²⁴ Ten adult patients who had an exacerbation of UC while maintained on oral mesalamine 2.4 g/day and who were intolerant of corticosteroid treatment were enrolled in the study. The patients were treated with rifaximin 400 mg twice daily for four weeks in addition to their mesalamine. Patients were evaluated before and after the study period using the Rachmilewitz Activity Index (RAI). All patients had a score of ≥ 9 at the beginning of therapy. Seven patients (70%) experienced a clinical remission, defined as a score of <6 on the RAI and were able to avoid the use of corticosteroids. The remaining three patients did have reduced RAI scores. No drug-related adverse effects were reported.

Shafirin and Johnson conducted a 16-week, open-label trial of rifaximin in 29 patients with mild to moderate Crohn's disease.²⁵ Adult patients with a CDAI score greater than 220 and less than 400 who were on stable doses of corticosteroids, 6-mercaptopurine or azathioprine were enrolled. Recent users of infliximab were excluded from the trial. Patients received rifaximin 200 mg three times daily for 16 weeks and kept diaries of stool consistency and frequency, abdominal pain, well-being, fever and use of antidiarrheal agents. The CDAI score was calculated at clinic visits once each month. Mean change in CDAI score, the primary efficacy endpoint, was a decrease from 278 ± 51 at baseline to 159 ± 102 at month four ($p=0.0001$). A 70-point decrease in CDAI score was achieved by 82% of the patients in the per-protocol population. At month four, 59% of patients were in remission, defined as having a CDAI score less than 150. The number of liquid or very soft stools, abdominal pain scores and general well being scores were significantly improved by week 4 ($p=0.0036$, $p<0.0001$ and $p<0.0001$, respectively). The most common adverse effects reported were abdominal pain, fatigue and headache.

Prantera et al. conducted a double-blind, randomized, placebo-controlled trial of two doses of rifaximin in 83 adult patients with Crohn's disease.²⁶ Patients with mild to moderate Crohn's disease defined by a Crohn's Disease Activity Index (CDAI) of 200-400 received rifaximin 800 mg once daily plus placebo once daily, rifaximin 800 mg twice daily or placebo twice daily for 12 weeks. Patients on corticosteroids, antibiotics or anti-TNF factors were excluded. CDAI scores were calculated at randomization and every two weeks thereafter. Clinical remission, defined as a CDAI score of <250 was achieved by 32% of patients in the rifaximin 800 mg/day group, 52% of patients in the rifaximin 1600 mg/day group and 33% of patients in the placebo group. Clinical response, defined as a reduction of the CDAI score by 70 or more points, was achieved by 48%, 67% and 41% of patients, respectively. The rifaximin groups did not differ sig-

nificantly from the placebo group in these measures. There were significantly fewer treatment failures among the rifaximin-treated patients compared to placebo. Rifaximin 1600 mg/day was significantly more likely to produce a clinical remission or clinical response than either placebo or rifaximin 800 mg/day in patients with a high level of C-reactive protein at baseline.

Rifaximin in combination with ciprofloxacin has been evaluated for the treatment of chronic refractory pouchitis.²⁷ Eight patients who had symptoms of active pouchitis lasting four weeks or more despite treatment with standard antibiotics (metronidazole or ciprofloxacin) received rifaximin 1000 mg twice daily plus ciprofloxacin 500 mg twice daily for two weeks. The patients had a Pouchitis Disease Activity Index (PDAI) score calculated before and after the treatment period. The median PDAI score was 12 (range=9 to 18) before treatment. Five patients were determined to be in a clinical remission (PDAI score=0) after treatment; two patients were improved (decrease in PDAI score of 3 points or more) and one patient was unchanged after treatment. The patients who responded to the treatment maintained adequate function of their pouches for a median of 30 months of follow-up (range=8 to 60 months). No drug-related adverse effects were reported.

DRUG INTERACTIONS

Rifaximin is an inducer of the cytochrome P450 isoenzyme 3A4 *in vitro*; however, interactions with drugs metabolized by CYP 3A4 are unlikely because of the low systemic absorption of rifaximin.² An *in vivo* study evaluating the effect of oral rifaximin on midazolam administered orally and intravenously found no differences in the pharmacokinetics of midazolam attributable to rifaximin. A second study found that rifaximin did not alter the pharmacokinetics of a single dose of ethinyl estradiol plus norgestimate.

ADVERSE EFFECTS

The most commonly reported adverse effects of rifaximin include headache, abdominal pain, nausea and constipation.² The incidence of specific adverse effects in placebo-controlled trials did not differ significantly from placebo.

MEDICATION SAFETY

Rifaximin could be confused with rifampin or the brand name, Xifaxan[®], could be confused with cefoxitin. Rifaximin is not effective for travelers' diarrhea caused by *C. jejuni* and its efficacy has not been proven in travelers' diarrhea caused by *Salmonella* or *Shigella* species.² Rifaximin should not be used when diarrhea is associated with fever or blood in the stool. Bacterial

overgrowth resulting in *C. difficile*-associated colitis is possible with antimicrobial use. There is potential for the development of rifaximin-resistant strains of bacteria; it is not known whether such strains would also demonstrate resistance to rifampin. However, organisms with high MICs to rifaximin generally have high MICs to rifampin.²

COST, DOSE AND HOW SUPPLIED

Rifaximin is available as a 200-mg oral tablet in 30-tablet and 100-tablet bottles. The AWP per tablet is \$4.13. For the treatment of travelers' diarrhea, a three-day course of 200 mg three times daily is recommended. A course of treatment would cost \$37.17. For the treatment of hepatic encephalopathy, the typical dose is 400 mg three times daily. The treatment periods in clinical trials for hepatic encephalopathy ranged from seven to 21 days, with a mean duration of 13 days, although no clearly defined endpoint has been defined. Treatment of one patient at 400 mg three times daily for 13 days would cost \$322.14.

CONCLUSION

Trials in travelers' diarrhea demonstrate the efficacy of rifaximin, but superiority to current standard treatments has not been shown. Rifaximin appears to be safe in the treatment of hepatic encephalopathy. Some studies indicate that it is also efficacious, but in others it is difficult to determine whether the therapeutic benefit is derived in part from the placebo. Rifaximin has not been determined to be superior to current standard therapies for hepatic encephalopathy. The absence of significant side effects, particularly when rifaximin is compared to metronidazole or neomycin, may prove to be advantageous. However, the safety of rifaximin for extended use, as may be required in hepatic encephalopathy, has not been established.

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TABLE 3. COMPARATIVE COSTS PER DAY OF TREATMENTS FOR HEPATIC ENCEPHALOPATHY (AWP)

Drug	Dose	Cost per day
Metronidazole tablets	250 mg every 8 hr	\$1.29
Lactulose syrup	30 g every 6 hr	\$6.60
Neomycin tablets	3 g every 6 hr	\$44.84
Rifaximin tablets	400 mg every 8 hr	\$24.80

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