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Preface

Emerging infectious pathogens, increasing antimicrobial resistance (mediated primarily through horizontal transfer of a plethora of mobile DNA transfer factors) and the appearance of diseases that decrease the host defense have increased the need for more effective and safe treatments. Antibiotics have an important place in the management of GI diseases. Antibiotic use in gastroenterology falls into three general settings: (1) GI infections (e.g. bacterial diarrhea, cholangitis, diverticulitis), (2) GI diseases that may involve infectious agents but are not ‘classic’ infectious diseases (e.g. H. pylori-positive peptic ulcer, IBD), and (3) antibiotic prophylaxis for GI procedures.

The proliferation of antibacterial agents has made the choice of antibiotics increasingly complex. Nonabsorbed oral antibiotic therapy, unlike systemically available antibiotics, allows localized enteric targeting of pathogens and is associated with a minimal risk of systemic toxicity or side effects. Compared to systemic drugs, the number of poorly absorbed antimicrobials that would best target the GI tract is relatively small and almost completely limited to aminoglycosides (neomycin). Indeed, both ototoxicity and nephrotoxicity have been reported after oral neomycin especially in patients with renal dysfunction. In order to overcome these limitations, a novel rifamycin derivative, rifaximin, with improved pharmacokinetic (i.e. virtually absence of GI absorption) and pharmacodynamic (i.e. with broad spectrum of antibacterial activity) properties has been synthesized. The aim of this review is to summarize the available pharmacology and safety data on this nonsystemic antibiotic as well to outline its current and potential clinical use.

Regards

Dr Amit Bhalla, MD
Medical Advisor
A. Infectious Diarrhoea

Introduction

Antibiotics have a recognized role in the treatment of culture-proven bacterial causes of symptomatic enteric infection such as Shigella spp., Campylobacter jejuni and Salmonella typhi. While fluid replacement remains the classic cornerstone of the treatment of diarrhea, empiric antibiotic treatment is logical in certain situations. Severe diarrhea is more likely to be associated with bacterial causes.

Definition

Diarrhoea is defined as watery or liquid stools, usually with an increase in stool weight above 200 g per day and an increase in daily stool frequency.

Aetiology

The cause depends on geographic location, standards of food hygiene, sanitation, water supply, and season. The commonly identified causes of sporadic diarrhoea in adults in developed countries include Campylobacter, Salmonella, Shigella, Escherichia coli, Yersinia, protozoa, and viruses, but no pathogens are identified in over half of patients. In returning travelers, about 80% of cases are caused by bacteria, such as enterotoxigenic E coli, Salmonella, Shigella, Campylobacter, Vibrio, enteroadherent E coli, Yersinia, and Aeromonas.
Enterotoxigenic Escherichia coli (ETEC)

Enterotoxigenic E. coli is a common cause of bacterial diarrhoea. Infection with ETEC is the leading cause of travelers' diarrhoea and a major cause of diarrhoeal disease in underdeveloped nations, especially among children. ETEC is transmitted by food or water contaminated with animal or human feces. ETEC causes a significant amount of illness worldwide.

Clinical features of E coli Diarrhoea

1. Profuse watery diarrhoea
2. Abdominal cramping
3. Fever
4. Nausea with or without vomiting
5. Chills
6. Loss of appetite
7. Headache
8. Muscle aches and bloating

Current management options and limitations

- Clear liquids are recommended for persons with diarrhoea to prevent dehydration and loss of electrolytes.
- Although antimotility agents (e.g., Lomotil) can effectively relieve ETEC-associated diarrhoea and cramps, they may prolong the time it takes the body to rid itself of the toxin.
- Antibiotics can shorten the duration of diarrhoeal illness and discomfort, especially if given early.
- ETEC is frequently resistant to common antibiotics, including trimethoprim-sulfamethoxazole and ampicillin.
Because resistance to antibiotics is increasing worldwide, the decision to use an antibiotic should be carefully weighed against the severity of illness and the risk of adverse reactions, such as rash, antibiotic-associated colitis, and vaginal yeast infection.

An ideal antimicrobial agent for the treatment of bacterial causes of infectious diarrhea would have the following features:

1. Excellent activity against a broad range of bacterial enteropathogens
2. Nonabsorbable
3. Favorable side effect profile
4. Efficacious in the treatment of infectious diarrhea
5. Major indication is enteric disease, and
6. Does not easily develop resistance or promote cross-resistance

B. Hepatic Encephalopathy

Introduction

Hepatic encephalopathy (HE) is a frequent and serious complication of cirrhosis that carries prognostic implications.

Pathogenesis and Classification

Clinical classification

The two elements that confer the name to the syndrome and intervene in its clinical classification are neurological disturbance and liver failure. Depending upon neurological manifestations, HE is classified as

- Episodic (previously acute)
- Persistent (previously chronic)
• Minimal (previously subclinical)[1]

Depending on the disease of the liver, HE is termed
• Type C (associated with cirrhosis)
• Type A (associated with acute liver failure)
• Type B (associated with portal-systemic bypass and no intrinsic liver disease)

Causes of HE
Irrespective of the characteristics of the neurological manifestations and the type of liver
disease, the link between them is that HE is caused by the effects on the brain of
substances that under normal circumstances are efficiently metabolized by the liver[2].
Ammonia remains as the most important factor in the pathogenesis of HE. Currently,
there is a better explanation of the mechanisms by which ammonia interferes with brain
function and a better recognition of the factors that influence these effects.

Role of Ammonia
Ammonia is generated in the intestines from different sources: nitrogenous components
of the diet, deamination of glutamine, and breakdown of urea by urease present in
colonic flora.[3]
Figure 1.

Interorgan ammonia trafficking and metabolism. Ammonia is generated in the intestines from nitrogenous compounds from the diet, deamination of glutamine by glutaminase, and metabolism of nitrogenous substances by colonic flora. In normal circumstances, most ammonia is metabolized to urea in the liver. Portal-systemic shunts and liver failure cause a rise in blood ammonia that may affect brain function by inducing several disturbances in astrocytes; these may impair mitochondria and the glutamate-glutamine trafficking between neurons and astrocytes. Skeletal muscle is capable of decreasing blood ammonia by metabolizing ammonia to glutamine. The kidney has also an important role in determining blood ammonia by excreting urea in the urine and generating ammonia. NH₃, ammonia; GLU, glutamate; GLN, glutamine; GNASE, glutaminase; BBB, blood-brain barrier.
Reappraisal of Current Therapies: Mainstays of Therapy

Since the finding that the administration of nitrogenous compounds could precipitate HE, the focus of therapy has been to reduce ammonia generated in the colon. Therefore, the mainstays of therapy have been the administration of antibiotics (neomycin, rifaximin, vancomycin), nonabsorbable disaccharides (lactulose, lactitol), and protein-restricted diets.[4]

Nonabsorbable disaccharides may not be effective

A meta-analysis investigated the effect of nonabsorbable disaccharides (lactulose or lactitol) compared with placebo, antibiotics, or no intervention. [5] The main result is that nonabsorbable disaccharides seem to reduce the risk of no improvement of HE, but are inferior to antibiotics. However, the results were not homogeneous and the analysis of the two high-quality trials (44 patients) that compared nonabsorbable disaccharides to placebo found no significant effect. These data have generated a controversy of whether or not nonabsorbable disaccharides should be used. Most authors agree that the data on the biological effects of these compounds and a large clinical experience are sufficient to justify their use.[6] The use of antibiotics to treat HE was reinforced by the meta-analysis. Nevertheless, antibiotics have secondary effects that may be severe, especially if administered for long periods. [7]

C. Acute Bacterial Gastroenteritis and Microflora in Irritable Bowel Syndrome

A complication of acute gastrointestinal infection is the subsequent development of irritable bowel syndrome (IBS). About a quarter of IBS patients recall an episode of acute gastroenteritis prior to the onset of their IBS. In a large prospectively conducted cohort study, the relative risk for developing IBS following bacterial gastroenteritis was 11-fold greater than that of the control population. [8]
SIBO as the underlying cause of IBS

The relationship between acute gastroenteritis and IBS may be due to either altered gut microbiota, bacterial overgrowth (SIBO), or a change in the part of the host as a consequence of an acute episode of gastrointestinal infection. There is a growing body of evidence pointing to SIBO as the underlying cause of IBS. There is also evidence of abnormal microbial fermentation in IBS patients as shown by increased excretion of microbially produced gases (hydrogen or methane) on the exhaled breath of IBS patients, compared with controls, after ingestion of lactulose, a nondigestible substrate during a lactulose breath test (LBT). Although prevalence of an abnormal lactulose breath test in IBS patients varies, in a randomized, placebo-controlled study of patients meeting Rome I criteria for IBS, the prevalence of an abnormal LBT was 84%. [9]

Role of Nonabsorbable antibiotics in IBS

Different breath test methods and instrumentation place the prevalence of an abnormal breath test in IBS patients in the range of 30-78%. Treating IBS patients with nonabsorbable antibiotics resulted in complete resolution of IBS symptoms in those patients who achieved a normalized breath test. [10] Similarly, in the RCT, patients reported 75% global improvement in their symptoms if they were randomized to the antibiotic group and their post-treatment breath test was found to be normal. The contribution of gut microbes to symptoms of IBS is further supported by the role of microbial gases in altered bowel patterns. In the RCT, the finding of breath excretion of methane alone was associated exclusively with constipation; and this observation was confirmed in a larger study. Furthermore, improvement of symptoms for patients with constipation-predominant IBS correlated with a reduction in methane production by neomycin.
Methane is a biologically active gas that is capable of slowing intestinal transit by shifting the pattern of motility from peristaltic to nonperistaltic. In a recent RCT, 87 IBS patients were given either rifaximin, a nonabsorbed oral antibiotic that acted primarily in the small intestine, or placebo. In this study, symptom improvement persisted through the entire 10-week observation period following discontinuation of the 10-day antibiotic treatment. Since symptom-directed treatment rapidly disappears upon cessation of treatment, such sustained improvement is only possible if the treatment were to be directed, instead, at the underlying cause of the symptoms of IBS and that cause were to be an antibiotic-sensitive mechanism such as SIBO. The relationship between SIBO and intestinal motility was supported by the finding of reduced frequency of cycling of interdigestive motility in patients with IBS. Impaired intestinal motility may be a key element in the loss of containment of the microflora, resulting in SIBO.

**Immune activation as a cause of SIBO and IBS**

The relationship between acute gastroenteritis, SIBO and IBS can be understood by considering the activation of host immunity by microbes and symptoms as consequences of immune activation. An additional piece of evidence supporting the idea of altered gut microbiota is the histological finding of immune activation in both IBS patients with a history of acute gastroenteritis and in IBS patients without such history.
Rifaximin: A Novel Nonabsorbed Rifamycin for Gastrointestinal Disorders

A. INTRODUCTION

Rifaximin is a semisynthetic derivative of rifamycin that was first approved in Italy in 1987, was approved by the US Food and Drug Administration (FDA) in 2004 for the treatment of uncomplicated traveler’s diarrhea, and is currently approved for use in 17 countries. Rifaximin’s additional pyridoimidazole ring makes it virtually nonabsorbable, enabling it to achieve a high concentration in the gastrointestinal tract and to be active against enteric infection or abnormal floral states.

The empirical formula is C43H51N3O11 and its molecular weight is 785.9. The chemical structure is represented below:

![Chemical Structure of Rifaximin]

B. MECHANISM OF ACTION

Rifaximin binds the beta subunit of the bacterial DNA-dependent RNA polymerase, inhibiting the initiation of chain formation in RNA synthesis.
C. PHARMACOKINETICS

Rifaximin is not inactivated by the gastric fluids, and it is poorly absorbed, with a bioavailability of <0.4% in the blood following oral administration. Approximately 97% of radiolabeled rifaximin is excreted in the feces as unchanged drug, with 0.32% of the dose detected in urine and without detectable levels in bile or breastmilk. After the oral administration of 400 mg twice per day for 3 days in travelers with diarrhea, rifaximin’s fecal concentration reached 8000 mg/g.

Less than 0.4% of an oral dose of rifaximin is absorbed. The following pharmacokinetics parameters were determined in 14 healthy subjects following a single oral dose of 400mg.
The pharmacokinetics of rifaximin 200mg TID for 3 days was also evaluated in 13 patients with shigellosis. After the last dose, Cmax ranged from 0.68-2.26 ng/ml and AUC0-last, was 7.83 ± 63.10 ng · h/mL. Dosage adjustments for hepatic dysfunction are not necessary, because of the minimal oral absorption, even in patients with hepatic encephalopathy. Likewise, dosage adjustments for renal insufficiency should not be a concern.

**Lack of Absorption**

An essential feature of an ideal antibiotic for infectious diarrhea is that it should not be absorbed. Among 18 adult volunteers who received a 400-mg dose, no rifaximin was detected in serum 4 h later in 9 subjects, and the highest detected levels in the remaining 9 subjects was 5.3 ng/ml. The mean recovery in urine from a 400-mg dose was 0.007% in the first 24 h with a negligible amount detected in the second 24 h after the dose. Furthermore, absorption of rifaximin is only minimally affected by colonic inflammation. Twelve subjects with mild to moderate ulcerative colitis took 400-mg doses. In only 4 subjects were levels ranging from 2 to 4.6 ng/ml noted irregularly, and 2 further subjects had single values of 13.4 and 22.4 ng/ml measured. The mean recovery in urine in the first 24 h was 0.009%. That rifaximin is virtually nonabsorbed is clear from these and other studies. The reason that this is potentially important is that adverse reactions can be predicted to be higher for drugs with systemic absorption.
D. ANTIMICROBIAL AND IN VITRO ACTIVITY

Rifaximin has broad-spectrum activity against aerobic and anaerobic gram-positive and gram-negative microorganisms.\textsuperscript{[15]}

In table 1, in vitro activity of rifaximin is shown as an MIC\textsubscript{90}, with a dosage of <64 \( \mu g/mL \) having activity against the majority of bacterial enteropathogens associated with diarrhea. The drug also has in vitro activity against Clostridium difficile, Helicobacter pylori, Yersinia enterocolitica, and Shigella species, with MICs that are 80–500 times lower than the concentration of rifaximin in the feces. Other gram-negative bacilli that are usually nonrelated to diarrhea (Klebsiella, Enterobacter, Proteus, Acinetobacter, and Pseudomonas species) demonstrated MIC\textsubscript{90} at levels between 4 and 128 \( \mu g/mL \). Rifaximin has a lower MIC against gram-positive bacteria, with an MIC\textsubscript{90} at dosages ranging from \( \leq 0.01 \) to 0.5 \( \mu g/mL \), than it does against methicillin-resistant Staphylococcus aureus (MIC\textsubscript{90}, 8–16 \( \mu g/mL \)) and enterococcus (MIC\textsubscript{90}, 4–16 \( \mu g/mL \)). The drug is also active against anaerobes, with an MIC\textsubscript{90} at dosages between 0.25 and 128 \( \mu g/mL \), and it is active against Gardnerella vaginalis, Mobilincus species, Cryptosporidium parvum, and Blastocystis hominis.
E. Clinical Studies

I. Infectious diarrhea & Traveler’s Diarrhea

Table 2 summarizes the published clinical trials of rifaximin therapy of traveler’s diarrhea. In the first study, rifaximin given at a dosage of 200, 400, or 600 mg 3 times per day for 5 days (n=55) achieved lower values for the time to the last unformed stool, compared with trimethoprim-sulfamethoxazole (TMP-SMX) given at a dosage of 160,800 mg twice per day for 5 days (n=18), although the reduction in illness was nonstatistically significant \[^{16}\]
Rifaximin has better efficacy vs. Trimethoprim-Sulphamethoxazole

Rifaximin has lower treatment failure rates than Trimethoprim-Sulphamethoxazole
Efficacy of Rifaximin in traveler’s diarrhea

In the second study, rifaximin given at a dosage of 400 mg twice per day for 3 days (n=93) was as effective as ciprofloxacin given at a dosage of 500 mg twice per day for 3 days (n=94).\textsuperscript{[17]}

Comparable efficacy to Ciprofloxacin
In the last multicenter, placebo-controlled trial, rifaximin given at a dosage of 200 mg (n=125) or 400 mg (n=126) 3 times per day for 3 days significantly shortened the time to the last unformed stool, compared with placebo (n=129). The number of unformed stools per 24-h period and the number of subjects considered to be healthy after receiving therapy were similar between subjects receiving rifaximin or ciprofloxacin. The rate of microbiologic cure associated with rifaximin was lower than the rates associated with TMP-SMX and ciprofloxacin, but greater than the rate associated with placebo. We feel that the important effect of an antibacterial drug in the treatment of traveler’s diarrhea is the reduction of illness, rather than the eradication of a pathogen from a nonsterile gut, especially in an environment where travelers do not represent the important reservoir of enteric pathogens.

Several uncontrolled clinical trials have suggested that rifaximin is an effective alternative for the treatment of infectious diarrhea in nontravelers. In an open-label study, 20 hospitalized adults with acute enterocolitis treated with rifaximin experienced clinical improvement, with an 80% pathogen-eradication rate. In a double-blind study, 121 elderly patients with diarrhea received rifaximin or placebo, with better reduction in

Table 2. Controlled clinical trials of rifaximin in the treatment of traveler’s diarrhea.

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<tr>
<td>Variable</td>
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<td>TMP-SMX</td>
<td>RFX</td>
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<td>Mexico</td>
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<tr>
<td>No. of subjects</td>
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<td>93</td>
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<td>Dosage</td>
<td>200 mg, 400 mg, or 600 mg 3 times per day</td>
<td>160 mg/800 mg twice per day</td>
<td>400 mg twice per day</td>
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<tr>
<td>Duration, days</td>
<td>5</td>
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<td>3</td>
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<tr>
<td>TLUS, median h</td>
<td>28.3, 40.5, or 35.0</td>
<td>47.0</td>
<td>25.7</td>
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<td>Rate of treatment failure, %</td>
<td>11.1</td>
<td>17.6</td>
<td>9.7</td>
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<tr>
<td>Rate of microbiological cure, %</td>
<td>80</td>
<td>100</td>
<td>74</td>
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NOTE: CIP, ciprofloxacin; NA, not available; RFX, rifaximin; TLUS, time to last unformed stool; TMP-SMX, trimethoprim-sulfamethoxazole.

* Defined as eradication in post-treatment samples of pathogens found in pretreatment samples.

** P<.05 comparing either rifaximin group with placebo.
the number of unformed stools and in the duration of symptoms in the rifaximin group. Although there are limited data regarding the effectiveness of rifaximin in children with bacterial diarrhea, and although rifaximin is not approved for use in children, a pediatric suspension form is available in some countries. The first study involving children with infectious diarrhea was conducted in 1984 and showed that rifaximin was significantly superior to placebo. In a small study of 46 children receiving antimicrobial prophylaxis for genito-urinary disorders with acute recurrent diarrhea, 93% of rifaximin-treated children experienced an improved condition, compared with 44% of children receiving oral rehydration alone. Finally, a study that compared rifaximin with rehydration in the treatment of 146 children with acute diarrhea showed reduction of the duration of diarrhea in the rifaximin group. On the basis of its in vitro activity, rifaximin is being evaluated for possible efficacy in the treatment of C. difficile–associated diarrhea. One small randomized study demonstrated similar efficacy in reducing the duration of diarrhea when either rifaximin or oral vancomycin was given to patients with C. difficile–associated diarrhea. 

II. Small bowel bacterial overgrowth and IBS.

Rifaximin improves abdominal distension, bloating and flatulence In a double-blind study, 34 patients with irritable bowel syndrome were randomized to receive rifaximin or activated charcoal. The rifaximin group experienced reduction in the production of Hydrogen, together with a decreased severity of symptoms and abdominal girth. There were no changes in bloating, abdominal pain, or production of Methane in either group.

Rifaximin resolves the malabsorption secondary to SIBO

Rifaximin may help to resolve the malabsorption secondary to small-bowel bacterial overgrowth, because of its bile-soluble and nonabsorbable properties. In a small,
randomized, doubleblind study, 10 patients received rifaximin at a dosage of 400 mg 3 times per day, and 11 patients received chlortetracycline at a dosage of 333 mg 3 times per day for 7 days. Normalization of breath-hydrogen test results occurred in 70% of rifaximin-treated versus 27% of tetracycline-treated patients (P<.01).
The Effect of a Nonabsorbed Oral Antibiotic (Rifaximin) on the Symptoms of the Irritable Bowel Syndrome

Alterations in gut flora may be important in the pathophysiology of the irritable bowel syndrome (IBS). The aim of this study was to determine whether the nonabsorbed antibiotic rifaximin is more effective than placebo in reducing symptoms in adults with IBS. A double-blind, randomized, placebo-controlled study was carried out at 2 tertiary care medical centers. 87 patients who met Rome I criteria for IBS and were enrolled from December 2003 to March 2005.

Participants who met enrollment criteria were randomly assigned to receive 400 mg of rifaximin 3 times daily for 10 days (n = 43) or placebo (n = 44). Eighty participants completed rifaximin therapy or placebo, and follow-up data were available for at least 34 participants per study group at any time point thereafter.

A questionnaire was administered before treatment and 7 days after treatment. The primary outcome was global improvement in IBS. Patients were then asked to keep a weekly symptom diary for 10 weeks. Over the 10 weeks of follow-up, rifaximin resulted in greater improvement in IBS symptoms (P = 0.020). In addition, rifaximin recipients had a lower bloating score after treatment.

Rifaximin improves IBS symptoms for up to 10 weeks after the discontinuation of therapy.
Rifaximin versus other antibiotics in the primary treatment and retreatment of bacterial overgrowth in IBS. [21]
Purpose: Previous studies demonstrate improvement in IBS after antibiotic therapy, with the greatest efficacy seen with the antibiotic, rifaximin. The purpose of this study was to compare the efficacy of rifaximin in both the treatment and retreatment of IBS. Methods: A retrospective chart review was conducted on Rome I-positive IBS patients. Charts were reviewed to evaluate all antibiotic treatments (rifaximin, neomycin, doxycycline, amoxicillin/clavulanate, and ciprofloxacin), even those predating 1 July 2004. Data collection included symptoms, breath test results (pre- and post-treatment), antibiotics used, and clinical response to individual antibiotic treatments before and after rifaximin availability in the USA. Results: Out of 98 eligible charts, 84 patients received one course of rifaximin. Fifty of these (60%) had a follow-up breath test. Among these, 31 (62%) were clinical responders and 19 (38%) were nonresponders. Of 31 responders, 25 (81%) had a normal follow-up breath test compared with only 3 of the 19 nonresponders (16%) (P < 0.001). Of participants given rifaximin, 69% (58 out of 84) had a clinical response compared with only 38% (9 out of 24) with neomycin (P < 0.01) and 44% (27 out of 61) with all non-rifaximin antibiotics (P < 0.01). Rifaximin was used as retreatment on 16 occasions, and all patients improved. Conclusions: Rifaximin is more effective than other antibiotics in the treatment and retreatment of IBS.

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<td>Condition (n of participants)</td>
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<tr>
<td>Initial treatment with rifaximin (84)</td>
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<td>Initial treatment with neomycin (24)</td>
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<td>Initial treatment with other nonrifaximin antibiotics (61)</td>
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III. Inflammatory bowel disease

*Antibiotic treatment of Crohn’s disease: results of a multicentre, double blind, randomized, placebo-controlled trial with rifaximin*

Clinicians often employ antibiotics in Crohn’s disease. Rifaximin is active against bacteria frequently found in the intestinal mucosa of Crohn’s disease patients. To evaluate the difference in efficacy between once and twice daily oral administration of rifaximin and placebo in the treatment of active Crohn’s disease. 83 patients with mild-to-moderate Crohn’s disease were enrolled and randomized to three treatments for 12 weeks: Group A (rifaximin 800 mg o.d. + placebo), Group B (rifaximin 800 mg b.d.) and Group C (placebo b.d.). Clinical remission was achieved by 52% of Group B, 32% (A) and 33% (C). Clinical response was seen in 67% (B), 48% (A) and 41% (C), without reaching a statistically significant difference. Treatment failures were: 4% (B), 12% (A) and 33% (C), (P ¼ 0.010). Remission and response rates of rifaximin 800 mg b.d. were significantly higher than those of placebo and rifaximin 800 mg o.d. in patients with elevated C reactive protein values (P < 0.05). Rifaximin 800 mg b.d. was superior to placebo in inducing clinical remission of active Crohn’s disease. Although this difference was not statistically significant, the number of the failures in the placebo group was significantly higher than those who received rifaximin 800 mg b.d.
IV. Hepatic encephalopathy.

Comparison of rifaximin and lactulose for the treatment of hepatic encephalopathy: a prospective randomized study. [22]

Rifaximin has been reported to be effective for the treatment of hepatic encephalopathy (HE) in Europe. However, it is unknown whether Rifaximin is effective for the treatment of HE in Koreans, therefore we conducted a open-label prospective randomized study to evaluate the efficacy of rifaximin versus lactulose in Korean patients. Fifty-four patients with liver cirrhosis and hepatic encephalopathy were enrolled. Thirty-two patients were randomized to receive rifaximin and 22 to receive lactulose both over a 7-day periods.
Before and at the end of treatment, gradation of blood ammonia, flapping tremor, mental status, number connection test (NCT) were performed and estimation of HE indexes determined. Both rifaximin and lactulose were effective in the majority of patients (84.4% and 95.4%, respectively, p = 0.315). Blood NH3, flapping tremor, mental status, and NCT was significantly improved by rifaximin and lactulose, and the post-treatment levels of these measures were similar for the rifaximin and lactulose-treated groups, as was the HE index (rifaximin group (10.0 --> 4.2, p = 0.000); lactulose group (11.3 --> 5.0, p = 0.000)). One patient treated with rifaximin complained of abdominal pain, which was easily controlled. There was no episode of renal function impairment in either treatment group. Rifaximin proved to be as safe and as effective as lactulose for the treatment of Korean patients with hepatic encephalopathy.
Several studies have demonstrated that rifaximin may be an alternative to current treatment options for hepatic encephalopathy. In a dose-ranging, randomized, double-blind study of 54 patients with cirrhosis that compared dosages of rifaximin at 200 mg, 400 mg, and 800 mg 3 times per day for 7 days, the 2 highest dosages demonstrated improvement of symptoms of hepatic encephalopathy and reduction of blood ammonia levels [23].

Three double-blind studies compared rifaximin at a dosage of 400 mg 3 times per day with lactulose for the treatment of hepatic encephalopathy. In those studies, improved cognitive function and reduction of ammonia levels favored rifaximin treatment, compared with treatment with lactulose. Rifaximin was shown to be comparable to neomycin in the treatment of hepatic encephalopathy. A randomized, double-blind, multicenter study comparing rifaximin with lactitol (dosage, 20 g 3 times per day) demonstrated similar efficacy for both drugs, with a more significant reduction of ammonia levels associated with rifaximin. However, neither rifaximin nor lactitol were beneficial in the prevention of hepatic encephalopathy following transjugular intrahepatic portosystemic shunt.

Cyclic treatment of chronic hepatic encephalopathy with rifaximin. Results of a double-blind clinical study.
Aim of the study was to comparatively evaluate the effect of rifaximin, lactitol and their combination in treating chronic HE. Forty out-patients (29 males, 11 females, mean age: 59 years, range 40-70), with viral liver cirrhosis and chronic HE (1st-2nd degree) were studied. HE was assessed by considering: mental state, asterixis, number connection test (NCT), arterial blood ammonia levels. Patients were randomly assigned to the following treatments: rifaximin (plus sorbitol as placebo) (group R); lactitol (group L); rifaximin plus lactitol (group RL). All treatments were continued for 15 days for 3 cycles, intervalled by 15 days of washout. Results: The 3 treatments reduced HE, but with different efficacy: patients of group R and RL significantly (p<0.05) documented a faster improvement in HE degree, a higher percentage of patients which normalized mental state and NCT, a faster improvement of asterixis and a longer persistence of normal ammonia levels than patients of group L. Conclusions: Rifaximin in combination with lactitol or sorbitol represents an effective and safe treatment of chronic HE.

Rifaximin in the treatment of hepatic encephalopathy

The objective of our investigation was to evaluate the safety and effectiveness of a new antibiotic used in this indication--rifaximin. With rifaximin, 400 mg three times per day, a total of 25 patients were treated for a 10-day period. Significant improvement of the manifestations of encephalopathy occurred (evaluated by the grade of encephalopathy, test of combining numerals, the degree of flapping tremor and the arterial ammonia level). None of the patients developed undesirable effects. Rifaximin seems an effective, safe drug for hepatic encephalopathy.

V. Diverticular disease

Some studies have suggested that rifaximin (in combination with fiber or mesalazine) could be beneficial in the treatment and prevention of nonsevere, uncomplicated diverticular disease, effecting a better and faster relief of symptoms and a lower incidence of diverticulitis, recurrence, and rectal bleeding.
VI. Role of Rifaximin in Colorectal surgery

Due to its pharmacokinetic and pharmacodynamic properties, rifaximin could be a suitable single oral agent for antibiotic prophylaxis in colorectal surgery. Indeed preoperative administration of 600 mg/daily or 800 mg/daily for 3 days significantly reduces fecal counts of both aerobic and anaerobic bacteria. In two studies rifaximin was compared to parenteral gentamycin or to oral paromomycin and proved to be equally effective in the prevention of infectious complications of colonic surgery. An additional trial evaluated the effect of adding rifaximin to intravenous cefotaxime (3 g daily for 5 days) in the prevention of bacterial infections after major colic surgery. Compared to the cephalosporin alone, the antibiotic combination was more effective. In all studies, rifaximin was tolerated extremely well. Nasogastric administration of rifaximin suspension (800 mg/day) for 5 postoperative days after colon surgery was attempted at a hospital and appeared to be as effective as preoperative oral administration in preventing infectious complications.

In summary, 3-day preoperative treatment with rifaximin appears to be an effective antibiotic prophylaxis for patients submitted to colorectal surgery. However, this kind of prophylaxis should be compared with the convenience and efficacy of perioperative regimens, such as those with an aminoglycoside or a cephalosporin, before gaining wider acceptance. Being perioperative antibiotics systemic drugs whose administration might be accompanied by adverse events, including life-threatening reactions, the use of a virtually unabsorbed antimicrobial would be the winner in terms of tolerability and safety. A large, double-blind clinical trial comparing different prophylactic regimens in the same population of patients is eagerly waited to definitely assess the potential of rifaximin in colorectal surgery.
F. Rifaximin & development of Resistance

Rifaximin Does Not Develop Resistance or Promote Cross-Resistance

While the emergence of rifaximin-resistant strains has been observed during the course of treatment, these strains disappear from the intestinal flora within 1–2 weeks of cessation of rifaximin. It has been shown that in vitro, the emergence of resistant Gram-positive flora could be induced, but the emergence of aerobic Gram-negative flora was rare [Schito, personal communication]. Furthermore, emergence of resistance was much less common under anaerobic conditions that mimic the environment of the gut. Also, subinhibitory concentrations of an antibiotic encourage the emergence of resistance, a situation much less likely to occur in the gut because of the huge concentrations of rifaximin in stool. Three studies have addressed the possibility of inducing cross-resistance to Mycobacterium tuberculosis during the use of rifaximin. In an experimental guinea pig model of M. tuberculosis, rifaximin was administered in an effort to induce resistance among M. tuberculosis strains of human origin. Not only did no resistance develop, crossresistance to rifampin also did not occur. In another approach, M. tuberculosis strains were subjected to subinhibitory concentrations of rifaximin. No induction of resistance or cross-resistance to rifampin occurred. \[23\]

Indications \[24\]

1. Infectious diarrhea (including TD)
2. Hepatic encephalopathy and Prevention of Spontaneous Bacterial Peritonitis in cirrhosis
3. Small Intestinal Bacterial Overgrowth
4. Irritable Bowel Syndrome
5. Inflammatory Bowel Disease
6. Colonic diverticular disease
Dosage and Administration

Administration
Rifaximin is administered orally without regard to meals.

Dosage
The usual dosage of rifaximin for the treatment of travelers’ diarrhea caused by noninvasive strains of E. coli in adults and adolescents 12 years of age or older is 200 mg 3 times daily for 3 days.

Rifaximin has been given in a dosage of 600–1200 mg daily (usually in 3 divided doses) for 7–21 days for the treatment of hepatic encephalopathy in adults.

Special Populations

In patients with hepatic impairment
Dosage adjustment is unnecessary in patients with hepatic impairment.

In patients with renal impairment
The pharmacokinetics of rifaximin have not been specifically studied in patients with renal impairment; however, clinically important changes in the elimination of rifaximin are not expected in those with renal impairment since the drug is poorly absorbed from the GI tract and is almost entirely excreted in feces as unchanged drug.

Others
The pharmacokinetics of rifaximin have not been specifically studied in pediatric patients or in geriatric patients 65 years of age or older.
The effects of gender on pharmacokinetics of rifaximin have not been specifically studied.
Cautions

Contraindications

Known hypersensitivity to rifaximin, other rifamycin anti-infectives, or any ingredient in the formulation.

Warnings/Precautions

Warnings

Treatment of Travelers' Diarrhea.

Rifaximin should not be used in the treatment of diarrhea complicated by fever or bloody stools or treatment of diarrhea suspected to be caused by pathogens other than E. coli (e.g., Campylobacter jejuni, Shigella, Salmonella).

If diarrhea worsens or persists more than 24–48 hours after initiating rifaximin, the drug should be discontinued and therapy with another anti-infective considered.

Superinfection/Clostridium difficile-associated Colitis.

Overgrowth of nonsusceptible organisms may occur. If superinfection occurs, appropriate therapy should be instituted. Treatment with anti-infectives may permit overgrowth of clostridia. Consider Clostridium difficile-associated diarrhea and colitis (antibiotic-associated pseudomembranous colitis) if diarrhea develops and manage accordingly.

Some mild cases of C. difficile-associated diarrhea and colitis may respond to discontinuance alone. Manage moderate to severe cases with fluid, electrolyte, and protein supplementation; appropriate anti-infective therapy (e.g., oral metronidazole or vancomycin) recommended if colitis is severe.
**Systemic Infections**
Rifaximin should not be used for the treatment of systemic bacterial infections since less than 0.4% of a dose is absorbed following oral administration.

**Sensitivity Reactions**
Hypersensitivity reactions (e.g., allergic dermatitis, rash, angioedema, urticaria, pruritus) reported.

**Specific Populations**

**Pregnancy**
Category C

**Lactation**
Not known whether rifaximin is distributed into human milk; discontinue nursing or the drug because of potential for adverse effects in infants.

**Pediatric Use**
Safety and efficacy not established in children younger than 12 years of age.

**Geriatric Use**
Experience in those 65 years of age or older is insufficient to determine whether they respond differently than younger adults.

**Common Adverse Effects**
Adverse effects occurring in 2% or more of patients receiving rifaximin in clinical trials include flatulence, headache, abdominal pain, rectal tenesmus, defecation urgency, nausea, constipation, fever, and vomiting.
Drug Interactions

Drugs Metabolized by Hepatic Microsomal Enzymes

Although in vitro studies indicate that rifaximin induces the CYP3A4 isoenzyme, drug interaction studies with midazolam or an oral contraceptive containing ethinyl estradiol and norgestimate did not demonstrate clinically important effects on drug metabolism. Pharmacokinetic interactions with drugs metabolized by this isoenzyme are unlikely.

Hormonal Contraceptives

Concurrent use of rifaximin (200 mg orally every 8 hours for 3 days) and a single dose of an oral estrogen-progestin combination contraceptive (ethinyl estradiol 70 mcg in fixed combination with norgestimate 500 mcg) did not substantially alter the disposition of ethinyl estradiol and norgestimate. No dosage adjustment necessary.
Conclusions

Rifaximin appears to be an ideal agent for the treatment of infectious watery diarrhea. It has shown excellent efficacy in numerous clinical trials of bacterial diarrhea. Its excellent safety profile and lack of systemic absorption predict that it should be useful in treating hosts for whom the currently favored fluoroquinolones are contraindicated. Uses limited to enteric indications and its inherently low propensity to induce sustainable resistance among Gram-negative flora favor the sustained usefulness of rifaximin in the treatment of enteric syndromes.
Salient Features of Rifaximin

1. Excellent efficacy in numerous clinical trials of bacterial diarrhea
2. Excellent safety profile
3. Lack of systemic absorption
4. Low propensity to induce sustainable resistance or cross resistance
5. Excellent activity against a broad range of bacterial enteropathogens
6. Major indication is enteric disease
7. Dosage adjustment not required in patients with hepatic impairment
8. Can be taken irrespective of the meals; with or without food.
References


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