


Post Marketing Observational Study of Fixed Dose Combination of Rifaximin and Metronidazole in The Management of Acute Diarrhea

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ABSTRACT

Background: Infectious diarrhea is endemic in many parts of the world. It is generally mixed in etiology involving viruses, bacteria, and parasites. Antibiotics belonging to fluoroquinolones class are most commonly used but are beneficial only in certain types of acute diarrhea with side effects like tendinopathy, arthropathy, neuropathy, arrhythmia, hypoglycemia, and hyperglycemia. Rifaximin with its unique mechanism, along with established metronidazole is proposed as a treatment option for acute diarrhea caused due to mixed gastrointestinal infections. This study aims to evaluate the efficacy and tolerability of a fixed-dose combination of rifaximin and metronidazole in the empirical management of acute diarrhea.

Method: An open-label, non-comparative, non-randomized, multicenter trial was conducted on 238 patients presenting with acute diarrheal episodes involving various etiologies. Since this is an observational study and was conducted post-approval of the drug by the state FDA, informed consent and ethics approval was not mandatory. Patients were given fixed dose combination tablet containing rifaximin 200 mg and metronidazole 400 mg twice a day for 5 days. Primary outcomes were a change from baseline in the number of soft or watery stools, fever, nausea, vomiting, abdominal pain, and gas/flatus at day 5.

Results: In the final analysis, 150 patients were included, as 88 patients were lost to follow-up. After 5 days of therapy, the mean number of watery stools per day was reduced from 7.133 ± 2.055 to 0.733 ± 0.833 (p < 0.0001). Side effects complaints such as gastritis (5.33%), nausea (10.66%), and metallic taste (3.33%) were reported.

Conclusion: A combination of rifaximin and metronidazole significantly reduces the number of watery stools and associated symptoms and is a clinically effective and safe option in the empirical management of acute diarrhea of various etiologies.

Keywords: acute diarrhea, mixed gastrointestinal infection, rifaximin, metronidazole

ABSTRAK

Latar Belakang: Diare akibat infeksi merupakan penyakit endemik di beberapa negara di dunia. Penyebab dari infeksi tersebut dapat beragam hingga multipatogen seperti virus, bakteri, dan parasite. Antibiotik golongan fluoroquinolone merupakan salah satu yang sering dipakai untuk kasus diare akut, akan tetapi memiliki beberapa efek samping seperti tendinopati, artropati, neuropati, aritmia, hipoglikemia, dan hiperglikemia. Rifaximin dengan mekanisme yang unik dibandingkan dengan metronidazole dianggap sebagai pilihan terapi untuk diare akut karena efek sampingnya lebih sedikit dibandingkan dengan antibiotik golongan fluoroquinolone. Rifaximin dan metronidazole dalam kombinasi tetap efektif dalam mengatasi kasus diare akut.

Metode: Penelitian ini adalah studi observasional terbuka, non-kontrol, non-randomisasi, dan multikeset. Penelitian dilakukan pada 238 pasien yang menderita diare akut dengan berbagai penyebab. Selama penelitian, 150 pasien yang dapat diikuti, sedangkan 88 pasien lainnya kehilangan dalam penelitian. Setelah 5 hari pengobatan, rata-rata jumlah buang air kencang per hari dikurangi dari 7.133 ± 2.055 menjadi 0.733 ± 0.833 (p < 0.0001). Serta adanya gejala khusus seperti gastritis (5.33%), mual (10.66%), dan rasa kacau (3.33%) yang dilaporkan.

Kesimpulan: Kombinasi rifaximin dan metronidazole efektif dan aman dalam pengobatan empiris diare akut akibat infeksi berbagai penyebab.

Kata kunci: diare akut, infeksi gastrointestinal, rifaximin, metronidazole
Metode: Studi open label, non-komparatif, tidak terandomisasi, multisenter ini dilakukan dengan melibatkan 238 pasien dengan diare akut yang diakibatkan berbagai etiologi. Karena studi ini merupakan studi observasional dan dilakukan menggunakan obat yang telah disetujui oleh badan FDA setempat, seterusnya pasien dan etik tidak diwajibkan. Pasien diberikan obat kombinasi dosis tetap dari rifaximin 200 mg dan metronidazole 400 mg dua kali sehari selama 5 hari. Keluaran utama dari studi ini adalah perubahan jumlah bab cair, demam, mual, muntah, nyeri perut, dan flatus pada hari kelima pengobatan dibandingkan dengan saat pertama kali berobat.

Hasil: Pada analisis akhir, terdapat 150 pasien yang diikutsertakan dimana 88 pasien diantaranya lost to follow up. Setelah 5 hari terapi, rata-rata jumlah bab cair per hari telah turun dari 7,13±2,055 menjadi 0,73±0,8333 (p<0,0001). Efek samping yang terjadi berupa gastritis (5,33%), mual (10,66%), dan rasa metalik (3,33%).

Simpulan: Kombinasi dari rifaximin dan metronidazole secara signifikan menurunkan jumlah bab cair dan gejala penyerta serta bersifat efektif secara klinis dan aman sebagai terapi empirik untuk diare akut yang disebabkan oleh berbagai etiologi.

Kata kunci: diare akut, infeksi gastrointestinal campuran, rifaximin, metronidazole.

INTRODUCTION

Diarrhea is defined as the passage of three or more loose or liquid stools per day (or more frequent passage than is normal for the individual). Acute diarrhea is a commonly diagnosed condition among adults, causing significant morbidity worldwide. While it is often viewed as a major cause of childhood mortality in developing countries, adult mortality resulting from diarrhea is also common, especially during outbreaks. Poor sanitation and unhygienic eating habits contribute to the high prevalence of acute diarrhea among adults, with contaminated food and water being the primary culprits. Diarrhea is most frequently caused by viruses, bacteria, and parasites, with fungi playing a minimal role, mainly in individuals with compromised immune systems. Common bacteria that cause diarrhea include *E. coli*, *Shigella* spp., *Salmonella* spp., and *Campylobacter* spp., while parasitic protozoa like *Giardia lamblia* and *Entamoeba histolytica* can lead to both temporary and chronic diarrhea. These parasites are known to spread widely because they are commonly found in food and water, and they exhibit resistance to to environmental factors and disinfection procedures. The scientific community, over the past few decades, has established a consensus on the most effective measures to reduce the incidence, morbidity, and mortality of acute diarrhea. Some of the measures aimed at reducing the incidence of diarrheal diseases include clean water supply, adequate treatment of human waste, education, and food safety. Therapeutic management with emphasis on oral rehydration therapy and intravenous rehydration therapy, recommended since the 1970s, are milestones of twentieth-century medicine. Since per capita income in India is low and most of gastrointestinal infections are mixed in nature, doctors prefer empirical therapy to ensure faster recovery without burdening the patient with additional investigations like stool culture.

Rifaximin is a semisynthetic derivative of rifamycin that acts by binding to the β-subunit of bacterial DNA-dependent RNA polymerase, resulting in inhibition of bacterial RNA synthesis. It has broad-spectrum activity against Gram-positive and Gram-negative aerobic and anaerobic bacteria. It shows activity against essentially all enteric bacterial pathogens, including *Clostridium difficile* and *Helicobacter pylori*. Being virtually unabsorbed, this antimicrobial has little value outside the area of enteric infections, thus minimizing both antimicrobial resistance and systemic adverse events. It has proved to be safe in all patient populations, including young children. Bacterial pathogens show a low potential for developing resistance during rifaximin therapy. When rifaximin resistance to gut flora did occur during therapy, the resistance was unstable. Rifaximin has surprisingly little effect on both Gram-positive and Gram-negative flora of the colon.

Metronidazole is an antimicrobial agent that has been used in clinical medicine for more than 45 years. It has been shown to be effective against protozoal infections, such as amebiasis and giardiasis. It has high activity against Gram-negative anaerobic bacteria, such as *B. fragilis*, and Gram-positive anaerobic bacteria, such as *C. difficile*. Metronidazole with its good activity against pathogenic anaerobic bacteria, favorable pharmacokinetic and pharmacodynamic properties and minor adverse effects is considered to be a cost-effective drug. In light of the above evidences, the current study proposes fixed-dose combination (FDC) of rifaximin and metronidazole as a useful
treatment option in the management of acute diarrhea and associated symptoms.

METHOD

Study Design and Patients

This study was an open-label, non-comparative, non-randomized, multicenter trial in 238 patients who visited panel doctors with acute diarrhea in 23 different clinics located in various parts of India. Patients (men and non-pregnant women) were eligible for this study if; they were suffering from acute diarrhea, aged > 18 years. We excluded patients with known/suspected history of hypersensitivity to any of the related drugs, colitis, gastrointestinal bleeding, known cases of renal or hepatic insufficiency, cardiac diseases, pregnant, or lactating women. Since this was an observational study and was conducted post-approval of the drug by the state Food and Drug Administration (FDA); informed consent and ethical approval were not mandatory.

Treatment and Duration of Treatment

Patients were given 1 tablet of Rifaxigyl-M® containing rifaximin 200 mg and metronidazole 400 mg twice daily for 5 days. Oral rehydrating solution was also prescribed according to the patient’s dehydration status. No other additional drugs were prescribed during the study.

Assessment of Primary Outcome Measure

The number of soft or watery stools, body temperature, nausea, vomiting, abdominal pain, and gas/flatus are parameters that were evaluated at baseline, day 3, and day 5 of the study.

Assessment of Secondary Outcome Measure

Efficacy and tolerability were evaluated based on the global assessment by the investigator on a 3-point scale marked as excellent/good/poor. Adverse events were recorded and the action taken was documented.

Statistical Analysis

Statistical analysis was done by “paired t-test” for each parameter compared with change from baseline to day 5. The minimum level of significance was fixed at 95% confidence limit and p < 0.05 was considered significant. All the statistical analysis was performed by using Graph Pad Prism 9 version 9.5.1.

RESULTS

A total of 238 patients were recruited in the study. 150 patients were included in the final analysis and 88 patients were lost to follow-up. A large number of patients were lost to follow up because there is a possibility that they recovered from illness and did not feel the need to report. The recruited patients were in the age range of 18 to 84 years (mean age 42.58 ± 12.26).

<table>
<thead>
<tr>
<th>Clinical symptoms</th>
<th>Baseline</th>
<th>Day 3</th>
<th>Day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>64 (42.66%)</td>
<td>4 (2.66%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>88 (58.66%)</td>
<td>16 (10.66%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>80 (53.33%)</td>
<td>13 (8.66%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>98 (65.33%)</td>
<td>15 (10%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Gas/flatus</td>
<td>56 (37.33%)</td>
<td>13 (8.66%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Number of Soft or Watery Stools

The number of stools per day was recorded at the start and end of the trial. Statistically significant reduction in the number of bowel movements was reported with rifaximin + metronidazole fixed-dose combination as compared to baseline. Number of stools per day reduced from 7.133 ± 2.055 to 0.733 ± 0.833 (p < 0.0001).

Other Parameters

Out of 150 patients, 42.66% patients reported fever, 58.66% reported nausea, 53.33% reported vomiting, 65.33% reported abdominal pain, and 37.33% reported gas/flatus at baseline. All the patients reported no symptoms at the end of the trial.

Safety Evaluation

Incidences of gastritis, nausea, and metallic taste were reported in 5.33%, 10.66%, and 3.33% of patients respectively. None of the patients withdrew from the study due to adverse events.

Global Assessment of Efficacy and Tolerability

As per investigators’ assessment of the efficacy of rifaximin + metronidazole fixed-dose combination, 63.33% of patients reported excellent, 36% of patients reported good, and 0.66% of patients reported poor efficacy. As per investigators’ assessment of the tolerability, 67.33% of patients reported excellent, 32% of patients reported good, and 0.66% of patients reported poor tolerability.
DISCUSSION

Diarrhea is the prevailing result of gastrointestinal tract infections, which typically have a multifaceted etiology. To effectively manage these mixed gastrointestinal infections, a combination therapy consisting of a broad-spectrum antibiotic and an antiprotozoal drug is a more rational approach. Cost is a concern even today and therefore doctors do not advise stool examination frequently and prefer empirical treatment with a combination covering bacteria and protozoa, as these are common ones because of unhygienic conditions prevailing in the country. This not only reduces the overall cost of therapy but also reduces the number of man days lost and consequently wages lost due to diarrhea.

Rifaximin has shown efficacy and tolerability in several clinical studies and systematic reviews which included patients with travelers’ diarrhea, small intestinal bacterial overgrowth (SIBO), diarrhea-predominant irritable bowel syndrome, and hepatic encephalopathy. Rifaximin has also shown therapeutic potential in the management of Clostridium difficile infection (CDI), especially in CDI recurrences. A good evidence supporting the use of rifaximin as a chemoprophylactic agent in travelers’ diarrhea, especially in individuals who are at high risk of severe complications from acute infectious diarrhea is available. Because rifaximin is non-absorbed, there is an absence of systemic drug interactions and the drug possesses an excellent safety profile due to limited potential for side effects. Therefore, this gut-selective antibiotic appears to be a promising agent for the treatment of acute infectious diarrhea and in chemoprophylaxis for travelers’ diarrhea.

It is found that in mixed gastrointestinal infections, 73% of patients were most often detected with protozoa including Giardia lamblia, Entamoeba histolytica, and Cryptosporidium spp. As metronidazole is still successfully used due to its efficacy against protozoal infections for the treatment of trichomoniasis, amoebiasis, and giardiasis, it should complement rifaximin in treating mixed infections.

In the present study, a combination of rifaximin and metronidazole significantly reduced the number of soft or watery stools. At the end of the study, all patients were afebrile. Symptoms associated with diarrhea such as nausea, vomiting, abdominal pain, and gas/flatus were significantly reduced after using rifaximin and metronidazole combination. None of the patients withdrew from the study due to adverse events. Minor incidences of gastritis, nausea and metallic taste were reported. Thus, based on available clinical studies and present clinical data, rifaximin in combination with metronidazole is a safe and effective option for the management of acute diarrhea due to mixed infections.

Limitation of the study: Although the combination is found to have a significantly favorable response, one of the major limitations of the study is that patients were not subjected to stool examination. The reason for not doing stool examination is that most of the time gastrointestinal infections is of mixed origin and subjecting the patients to get the stool examination is an additional cost to the patient in the prevailing low per capita income of the majority of the household. The study results would have been more unbiased if a routine stool examination was performed to rule out diarrhea due to exclusive viral origin; a self-limiting illness.

CONCLUSION

Acute diarrhea is a serious concern in India. In a quest for an effective and safer combination for acute diarrhea, FDC of rifaximin and metronidazole can be a new armamentarium in the management of acute diarrhea. A combination of rifaximin and metronidazole significantly reduced the frequency of diarrhea and other associated symptoms with excellent efficacy and tolerability. Therefore, FDC of rifaximin and metronidazole is an innovative safe and effective option for the management of acute diarrheal episodes.
ACKNOWLEDGEMENT

Author acknowledges the contribution of Mr. Rafique Sheikh, M. Pharm (Pharmacology), and Ms. Richa Deliwala, M. Pharm (Pharmacology) for their contribution in doing literature search & helping in the preparation of manuscript.

REFERENCES


