EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 11
Issue: 10
313-317
Year: 2024

THE EFFECT OF RIFAXIMIN AND NEOMYCIN ALONE, AND IN COMBINATION FOR THE SYMPTOMS OF SMALL INTESTINAL BACTERIAL OVERGROWTH-IRRITABLE BOWEL SYNDROME: A PATHOPHYSIOLOGY APPROACH

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Article Received on 22/08/2024 **Article Revised on 12/09/2024** **Article Accepted on 02/10/2024**

ABSTRACT
Irritable bowel syndrome (IBS) is a prevalent functional gastrointestinal disorder characterized by abdominal pain and altered bowel habits, affecting approximately 11% of the global population. The condition can manifest in various forms, including IBS with diarrhea (IBS-D), IBS with constipation (IBS-C), mixed bowel habits (IBS-M), and unclassified symptoms (IBS-U). Recent studies have implicated small intestinal bacterial overgrowth (SIBO) as a potential contributing factor to IBS, suggesting that dysbiosis in the gut microbiome may exacerbate symptoms. This review examines the therapeutic roles of antibiotics, specifically rifaximin and neomycin, in managing IBS symptoms associated with SIBO. Rifaximin, a non-absorbable broad-spectrum antibiotic, has shown significant efficacy in alleviating IBS symptoms by acting locally in the gut and reducing mucosal inflammation. Clinical trials indicate that rifaximin treatment results in a notable improvement in global symptom relief compared to placebo. Neomycin, while effective against specific bacterial strains, presents challenges due to its potential side effects and limited normalization rates in breath tests for SIBO. Combining rifaximin and neomycin may enhance treatment outcomes by leveraging the strengths of both antibiotics. Studies indicate that this combination therapy not only improves clinical symptoms more effectively than monotherapy but also leads to higher rates of SIBO eradication. Furthermore, a deeper understanding of the pathophysiological mechanisms underlying IBS—particularly the interactions within the brain-gut axis, genetic predispositions, and gut microbiota—can inform more targeted and effective treatment strategies. This review underscores the importance of recognizing the multifactorial nature of IBS and the need for tailored therapeutic approaches that consider both microbial imbalances and individual patient experiences. Future research should focus on optimizing antibiotic regimens and exploring additional therapeutic modalities to enhance patient outcomes in IBS management.

KEYWORDS: IBS, SIBO, Rifaximin, Neomycin, Combination Antibiotics.

INTRODUCTION
Irritable bowel syndrome IBS is a functional bowel disorder it is associated with alternative bowel habit, seriously effects on patient social life, irritable bowel syndrome is most prevalent FGID (Functional gastrointestinal disorders) noted in the general population in world wide. Irritable bowel syndrome is a chronic gastrointestinal disorder that is characterized by the abdominal pain, diarrhea, constipation, sometimes it occurs the both, mucous discharge along with stool and change in the form of appearance of stool.[1]

IBS is a type of disorder generally effect a part of gastrointestinal track with chronic, sporadic, and unpredictable symptoms there is disturbance in bowel function. IBS is common as many as 10-15% of the people in the united state have it affect twice as many females as males. Suggests that microbes present during infection gastroenteritis may trigger a long term reaction. IBS cause there symptoms without causing any visible damage to the digestive track. Research are refers to IBS with diarrhea as IBS-D, if IBS caused for Constipation is refers to IBS-C. if IBS cause the both diarrhea and constipation refers to mixed bowel habits IBS-M, and someone it indicate unknow type of symptoms of IBS-U. Healthcare profession refers IBS-A which standard for alternating bowel habits. The signs and symptoms of IBS

may very from person to another person and often mimic symptom of other conduction.

The most common symptoms of IBS includes; changes in bowel habits, abdominal pain and cramping, which often reduces after passing a stools, a feeling that the bowel are not empty after passing stool, swelling or bloating of the abdomen. The symptoms in men are experience more diarrhea, while the women's are experience more constipation. The symptoms that occur in children mostly commonly experience in the abdomen, which often occurs around bowel movements, and changes to their bowel movements such as diarrhea, constipation or both.[2]

Approximately 11% of people worldwide suffer with IBS. About thirty percent of persons with IBS symptoms will see a physician about their problems. Global prevalence rate of IBS vary between 1.1% and4.5% based on the population studies from countries world wide with a pooled global prevalence of 11.2% (95%CI:9.8-12.8) prevalence rate of 5-10% are reported form most European countries.[3] Most studies addressing prevalence of IBS are community surveys, with the majority from Europe, Southeast Asia, and North America. South America has the highest percentage (21.0%) while South Asia has the lowest (7.0%). according to reports on epidemiology.[4]

Antibiotics used for sibo associated with irritable bowel syndrome symptoms alone use of rifaximin

Rifaximin is a non-absorbable, (which do not interactive with systemic circulation in lumen of intestine) broad spectrum antibiotic mainly used to treat for traveler's diarrhea.it is a based on the rifamycin antibiotics family. Rifaximin is acts locally in the gut. It shows action on both aerobic and anaerobic gram-positive and gram-negative organisms. Moreover, intestinal protozoa-induced infections that lead to Cryptosporidium and Blastocystis are well treated by rifaximin. Rifaximin act to binding to the β subunit of the bacterial DNA dependent RNA polymerase resulting it inhibition of bacterial RNA synthesis and rifaximin has activity against a variety of enteric bacteria. Rifaximin acts locally with in the gastrointestinal track and has negligible absorption after orally administration. In the urine, less than 0.01% of the unaltered drug is eliminated. The minimal risk of toxicity or side effects. Because rifaximin is a hydrophobic medication and is insoluble in water, its bioavailability varies throughout the gastrointestinal system. The multifactorial mechanism of rifaximin is improve of symptoms in IBS. By using a rat model for visceral hyperalgesia, they measured visceral hyperalgesia, gut permeability, and microbial DNA in the ileum and found that oral rifaximin decreased the overall quantity of bacteria and alternation composition in the ileum. Rifaximin is decreased mucosal inflammation, measured by decreased level of levels of interleukins and tumor necrosis factor α (TNF-α) as well as visceral pain in response to chronic stress psychological.

In a randomized double- blind placebo-controlled trail of 124 patients with functional gastrointestinal symptoms the studies show the efficacy of rifaximin 400 mg twice daily vs placebo for 10 days on IBS and non-IBS patients. The patients used rifaximin least 12 weeks of active symptoms, including bloating, abdominal pain and discomfort, excessive flatulence and disturbances in bowel movements, feeling of incomplete evacuation, or abnormal stool consistency. Patient used for a total of 30 days. The patients recorded daily symptoms including abdominal pain or discomfort, distension, frequency of bowel movement, stool consistency, and feeling of incomplete evacuation, rifaximin produced significant improvement in global symptom. alleviation in the subgroup of IBS-positive individuals (40.5% vs 18.2%, P=0.04) as compared to placebo (41.3% vs 22.9%, P=0.003). treatment with rifaximin was also associated with improvement in abdominal bloating, distension, and flatulence for the symptoms of IBS.[5]

Alone use of neomycin

Neomycin is an aminoglycoside derivative antibiotic it shows bactericidal activity against gram-negative aerobic bacilli and some anaerobic bacilli where resistance has not yet arisen. Neomycin was first discovered in 1949 by microbiologist Selman Waksman and his student Hubert lechevalier at Rutgers university.

Neomycin action on 30S ribosomal subunit, impeding bacterial protein synthesis. Although the initial stages required for peptide synthesis is proceed without interruption, the subsequent elongation process is hindered due to the disruption of translational accuracy. Due to disturbances in the bacteria's translation process. Its act as bactericidal effect some adverse effect of neomycin is include nausea, diarrhea, and the risk of Clostridioides difficile–associated diarrhea. More severe adverse events of neomycin include nephrotoxicity, auditory ototoxicity, and vestibular ototoxicity, with the latter two often leading to irreversible effects.[6]

Clinical research has shown that treating SIBO with antibiotics reduces or eliminates IBS symptoms. In a single, double-blind, randomized, controlled trail in 111 patients, neomycin is used to treated patient were more likely to experience a 50% improvement in global IBS symptoms compared with placebo treated patients (43% vs23%; $p<0.5$). in the study,78% of IBS patients had an abnormal lactulose breath test result consistent with SIBO, and eradication of SIBO with neomycin led to an even greater response rate.

Using neomycin as a therapy for IBS. first Previously mentioned double-blind study, 25% of subject who take neomycin failed to normalize their breath test abnormalities, second, neomycin produces rapid and durable evidence of clinical resistance. Recent study,

75% of patients who take neomycin don't respond to subsequent therapy. On the neomycin are historically interesting as apart of initial examination of the role of gut bacteria in IBS this antibiotic does not have the ideal properties need to facilitate a gut-flora treatment approach to IBS. The above data that support the efficacy of neomycin for the testing SIBO and IBS. Neomycin use to reduced the symptoms of IBS, due to its nonabsorbable, be effective at improving IBS symptoms and have gut specificity, a low bacterial resistances profile.[7]

Combination of Rifaximin and Neomycin for irritable bowel syndrome

Sensitive intestinal syndrome An overabundance of bacteria in the small intestine has been connected to IBS (small intestinal bacterial overgrowth). Subjection with SIBO having similar symptoms to IBS, such as bloating, abdominal pain, and alternative bowel habits SIBO may be diagnosed by non-invasive breath test. It is indirect measure of bacteria overgrowth testing, through lactulose fermentation bacteria produce gases such as hydrogen and methane. Bacterial fermentation is the source of these gases in humans. The elevated levels of the gases early on the breath test it has be reported that 78% of subjects with IBS have a positive lactulose breath test (LBT), suggesting the presence of the SIBO.

In randomized controlled studies evaluating the use of the antibiotics, they observed to improve IBS. In the trail: 1 Neomycin improved IBS symptoms, it was to seen to normalize the breath test only 20% of the time. Another one rifaximin, a gut -selective nonabsorbable antibiotic, had higher eradication rates in bacterial overgrowth. Eradication rates of bacterial overgrowth using the patient using rifaximin has been seen in as high as 70% of the patient, and recent controlled study, rifaximin improved IBS symptoms.

There are three types of antibiotics are used in the treatments type 1 of the following antibiotic treatment: 500mg used in the Bis in die for 10 days of alone one of neomycin. 400mg tri in die for the 10 days of alone use of rifaximin, or a combination of rifaximin and neomycin for the 10 days.

Each patient was reviewed to evaluate the subjects' demographics and bowel symptoms in medication history. The data was recorded on the baseline breath test results (hydrogen & methane) the type of antibiotics treatment rifaximin and neomycin or in the combination of rifaximin and neomycin clinical response from is also observed. The clinical notes were examined to determine if the patients was clinically satisfied with their antibiotics treatment and if antibiotics are normalized the lactulose breath test (LBT), through eradicating the methane on the LBT. In most cases, subjects were seen within 2weeks of completion of antibiotics.

The clinical data analysis, the overall IBS improvement of the combination group of rifaximin and neomycin, while individually with rifaximin only group and neomycin only group. In additional, the rifaximin group was compared with neomycin group. The same group were compared for methane Eradication on breath test subjects who had a failed initial response to rifaximin and the subjects received rifaximin and neomycin combination treatment were also analyzed to evaluate their breath test are normalization. The data is provide evidence in the combination of rifaximin and neomycin antibiotic treatment in both clinical improvement and eradication of methane. Comparing with either neomycin or rifaximin alone.

The clinical response of rifaximin and neomycin treatment was observed the highest clinical response when compared the patients taking rifaximin only, or neomycin only; 85% of subjects received the rifaximin and neomycin combination has clinical response. If the subjects only receiving neomycin, the clinical response is 63%, where subject is only receiving rifaximin the clinical response is 56% by the compare. the clinical response of the combination rifaximin and neomycin work efficiently on methane elimination.[8]

Pathophysiology in irritable bowel syndrome

Irritable bowel syndrome centred on alternations of gastrointestinal motility and visceral sensory function. However, the despite the fact that alterations in the motor and sensory function are likely to be relevant for the manifestation of symptoms, the role of several mechanisms has been explored, including disorders of the gut-brain axis, genetic factors, gut microbiota, small intestinal bacterial overgrowth.

1. Brain-gut axis disorder

The evidence of IBS symptoms that is not relate to the gastrointestinal track, most of unnotably anxiety and depression, are highly prevalent in outpatient and community samples, the IBS as a primary disorder of brain-gut axis disfunction or even primary somatisation, the brain driving the gut manifestation, fatigue, and other complaints.[9] the brain-gut axis constitutes the enteric nervous system (ENS) and the gut wall is periphery, the CNS, and hypothalamo-pituitary adrenal axis. The bi-directional communication between the gut and central nervous system (CNS) is based on the neural, endocrine and neuroimmune pathways.

Signals from the GI tract affect the brain in a physiological state, and the brain can then affect immunological activity, secretion, and motility. For the correct management of food intake, digestion, gut feelings, and control of bowel movement, this axis is an essential communication mechanism. GI diseases are the result of anatomical and functional disturbances in the brain-gut axis, which alter the nervous system's perception and reflexive reactions.[10]

2. Genetic factor

The symptoms of IBS would offer more proof that the condition is genetically predisposed. IBS has been shown in many studies to cluster in families. even strong Evidence of familiar of IBS comes from larger, population-based studies. The study of residents un Olmsted county, the reporting a first -degree relative with abdominal pain or bowel problems was significantly associated with reporting of IBS symptoms.

A traditional method for estimating a disease's genetic and environmental components is twin studies. Concordance rate of a trail or disease are compared within and between monozygotic twins to estimate the genetic and environmental contribution. Because monozygotic twins share the same genetic and environmental contributions, a comparison may be done. The comparison can be made up, but dizygotic twins share only 50% of their genes. High concordance rates in monozygotic twins compared with dizygotic twins imply a strong genetic basic for the disease, and the presence of any discordance between monozygotic twins. The twin studies is provide support for the both genetic and environment bases.[11]

3. Gut microbiome

The gut microbiome comprises a myriad of intestinal microbes, it including viral bacteria, fungi, and protozoa that co-exist in imparting specific functions of dietary nutrient and drug metabolism, and maintenances of the gut mucosal barrier structure integrity and immunomodulation of the protection against pathogens. The imbalance of the gut flora may lead to a process is called dysbiosis and can occur through the loss or overgrowth of particular organism. The recent evidence the gut dysbiosis may contribute to the pathogenesis of IBS. The organisms that normally colonize the gut modulate signaling molecules and metabolites that are maintaining gut homeostasis and development of the mucosal immune system. Even light changes in the gut microbiome can lead to inflammatory changes that trigger oxidative stress, increase intestinal permeability and may lead to bacterial translocation across the mucosal surface. The gut microbiome composition in IBS patients. The recently identified in the gut microbiome that may be associated with severe IBS characterization of the IBS intestinal microbiome. A meta-analysis is found in the patient's lower level of lactobacillus and Bifidobacterium, as well as Escherichia Coli and Enterobacter in subjects in the gut microbiome analysis of patients with IBS compared to healthy controls.[12]

4. Small intestinal bacterial overgrowth

Studies indicate that the small intestinal bacterial overgrowth (SIBO) is frequent in IBS, the SIBO is primary cause of IBS all slobs, because of get involved clarification are realistic and suatanible. Moreover, the data indicate that the test used to promulgate the SIBO hypothesis in the lactulose hydrogen breath test may not have measured SIBO in the first place. They do not have any evidence of SIBO being absent before IBS symptoms and present after IBS emerges.[13]

The small intestinal bacterial overgrowth (SIBO) is a form of quantitative alternation of small bowel microbiota (dysbiosis) does not necessarily means SIBO only. The dysbiosis includes qualitative alternative of gut flora but also quantitative change small intestinal bacterial overgrowth. SIBO has been recognized by several experts. In SIBO, bacterial fermentation of diet in the lumen produces hydrogen and methane, carbon dioxide gases which may contribute to symptoms like distension, flatulence, abdominal pain, and bloating. Methane is slow gut transit resulting in constipation. SIBO is more often associated with diarrhea that constipation-predominant IBS. The mechanism of diarrhea in patient with SIBO includes de-conjugation of bile salt, enterotoxic effect of bacterial metabolites, increased small intestinal permeability, deficiency of vitamin B_{12} and low grade inflammation in the mucosa of the small intestine caused by immunological activation.[14]

Types of breath tests

Breath tests are inexpensive, simple and non-interfering, breath test which are can be used for 1. Spotting of excess bacteria in the small intestine 2. Evaluation of carbohydrate malabsorption/ maldigestion 3. Estimation of small intestinal transit time. To diagnose irritable bowel syndrome.

Breath testing consists of measurement of hydrogen/ methane gases production by bacterial fermentation of unabsorbed carbohydrate that is ingested by the subjects. Subsequent breath samples are collected at specific time intervals. (Every 15 or 30 minutes for 2-5 hours). The breath samples are analyzed using the SC Microlyser to measure amount of exhaled hydrogen and methane gases exhaled in the breath are generally the end result of fermentation of carbohydrate ingested by bacteria in intestine. Carbon dioxide is produced by all cells during metabolism, but the only bacteria and /or methane are produced in the body, this proves that a substrate has been exposed to intestinal bacteria with leading to bacterial fermentation.

Type of breath tests

Breath tests are is commonly used for the diagnosis of lactose malabsorption. Glucose breath test used for the small intestinal bacterial overgrowth and the lactulose breath test for orocecal transit time.

Glucose breth test

In physiological conditions, glucose is instantly absorbed in the small intestine. Yet, if there is a bacterial overgrowth in small intestine and bacterial fermentation of glucose leading to the production of hydrogen can take place earlier to the absorption of glucose, which is measured by increase in hydrogen and methane

concentration. The greater than 10 ppm in hydrogen and methane concentration in two successive readings above the apparent value is to be considered as significant and indicates the SIBO.

Lactulose breath test

Lactulose is disaccharide. Generally, there is no lactulose enzyme in the small intestine to hydrolyze this sugar, there it is transported tom the colon where it is metabolized by the colonic bacteria. The end point of the metabolism it includes production of hydrogen and methane. The time interval between swallowing of lactulose and rise in breath hydrogen and methane concentration greater than 10 PPM.

Lactose breath test

Lactose intolerances is prevailing throughout the world. Generally milk and other diary products avoided to improve their symptoms. For effective utilization of lactose requires hydrolysis by the enzyme lactase. An increase in the hydrogen and methane concentration greater than 20 PPM.

Fructose breath test

The test determination of individual has many problems in fructose digestion. Individuals with fructose intolerance may the symptoms like gas, diarrhea, bloating and cramping fructose occur as simple sugar in the fruits, vegetables, and honey. When fructose come in the comes in contact with normal bacteria in the intestine, hydrogen and methane greater than 20 PPM.[15]

CONCLUSION

In conclusion, Irritable Bowel Syndrome (IBS) is a complex and prevalent functional gastrointestinal disorder that significantly impacts the quality of life for many individuals worldwide. Characterized by symptoms such as abdominal pain, altered bowel habits, and bloating, IBS affects a substantial portion of the population, with varying prevalence rates across different regions. The condition is intricately linked to factors like the gut-brain axis, genetic predispositions, gut microbiota imbalances, and small intestinal bacterial overgrowth (SIBO).

Antibiotic treatments, particularly the use of rifaximin and neomycin, have emerged as promising options for alleviating IBS symptoms, especially in cases associated with SIBO. Rifaximin's localized action in the gut and minimal systemic absorption offer a low-risk therapeutic alternative, while neomycin, despite some adverse effects, shows significant symptom improvement in clinical studies. Recent findings suggest that a combination of rifaximin and neomycin may yield enhanced clinical responses and better eradication rates for methane-producing bacteria, further supporting its efficacy in treating IBS.

Understanding the multifaceted nature of IBS and the mechanisms at play is crucial for developing effective treatment strategies. Continued research into the pathophysiology of IBS, along with advancements in diagnostic testing such as breath tests, will be essential in tailoring personalized approaches for managing this challenging disorder. As we improve our grasp of IBS, we pave the way for better patient outcomes and enhanced quality of life for those affected.

REFERENCE

1. Vahedi H, Ansari R, Mir Nasseri MM, Jafari E. Irritable bowel syndrome: A review article. Middle East J Dig Dis, 2010; 2: 66-77.
2. Trull K, Brazier Y. All you need to know about irritable bowel syndrome (IBS). Medical News Today, 2023.
3. Enck P, Aziz Q, Spiller R, et al. Irritable bowel syndrome. Nat Rev Dis Primers, 2016.
4. Canavan C, West J, Card T. The epidemiology of irritable bowel syndrome. Clin Epidemiol, 2014; 6: 71-80.
5. Lorio N, Malik Z, Schey R. Profile of rifaximin and its potential in the treatment of irritable bowel syndrome. Clin Exp Gastroenterol, 2015.
6. Veirup N, Kyriakopoulos C. Neomycin.
7. Basseri RJ, Weitsman S, Barlow GM, Pimentel M. Antibiotics for the treatment of irritable bowel syndrome. J Gastroenterol Hepatol, 2011; 455-493.
8. Low K, Hwang L, Hua J, Zhu A, Morales W, Pimentel M. A combination of rifaximin and neomycin is most effective in treating irritable bowel syndrome patients with methane on lactulose breath test. J Clin Gastroenterol, 2010; 44: 547-550.
9. Holtmann GJ, Ford AC, Tally NJ. Pathophysiology of irritable bowel syndrome. Lancet Gastroenterol Hepatol, 2016; 1: 133-146.
10. Fichna J, Storr MA. Brain-gut interactions in IBS. Front Pharmacol, 2012.
11. Saito YA, Petersen GM, Locker III GR, Talley NJ. The genetics of irritable bowel syndrome. Clin Gastroenterol Hepatol, 2005; 3(12): 1057-1065.
12. Shaikh SD, Sun N, Canakis A, Park WY, Weber HC. Irritable bowel syndrome and the gut microbiome: A comprehensive review. J Clin Med, 2023; 12.
13. Saha L. Irritable bowel syndrome: Pathogenesis, diagnosis, treatment, and evidence-based medicine. World J Gastroenterol, 2014; 20(22): 6759-6773.
14. Ghoshal UC, Shukla R, Ghoshal U. Small intestinal bacterial overgrowth and irritable bowel syndrome: A bridge between functional and organic dichotomy. Gut Liver, 2017; 11(2): 196-208.
15. Rana SV, Malik A. Breath tests and irritable bowel syndrome. World J Gastroenterol, 2014; 20(24): 7587-7601.