—Case Reports—

Efficacy of Mirtazapine on Irritable Bowel Syndrome with Anxiety and Depression: A Case Study

Fumiaki Akama, Katsunaka Mikami, Natsuru Watanabe, Keitaro Kimoto, Kenji Yamamoto and Hideo Matsumoto

Department of Psychiatry, Tokai University School of Medicine, Kanagawa, Japan

Irritable bowel syndrome (IBS) is a disease in which gastrointestinal symptoms-primarily abdominal pain or discomfort and abnormal bowel movements persist chronically. For patients with IBS, mental illness, especially depression and/or anxiety, leads to a further lower quality of life. The purpose of this case study was to investigate the effects of mirtazapine (MIR) on mental health and IBS symptoms in a case of IBS accompanied by anxiety and a depressive state. This case report suggests that MIR is efficacious for the treatment of IBS with predominant diarrhea accompanied by depression and anxiety. (J Nippon Med Sch 2018; 85: 330–333)

Key words: irritable bowel syndrome, antidepressant, depression, anxiety, diarrhea, gut-brain axis

Introduction

Irritable bowel syndrome (IBS) is a disease in which gastrointestinal symptoms-primarily abdominal pain or discomfort and abnormal bowel movements (constipation or diarrhea)-persist chronically. However, IBS is not accompanied by organic abnormalities that explain the symptoms. IBS can be diagnosed according to the diagnostic criteria outlined by Rome IV and is classified by stool abnormality into the following types: IBS with predominant constipation, IBS with predominant diarrhea, IBS with mixed bowel habits, and IBS unclassified[1]. The prevalence of IBS is approximately 10% of the population[2]. IBS itself markedly lowers quality of life (QOL), and 42% to 61% of patients with IBS exhibit comorbid mental health concerns[3]. The comorbidity rate of IBS in patients with mental health conditions is 26.8% to 29.4% for major depressive disorder, 16.7% to 46.3% for panic disorder, and 37% for generalized anxiety disorder[4]. These high comorbidity rates further lower QOL. The purpose of this case study was to investigate the effects of mirtazapine (MIR) on mental health symptoms and IBS symptoms in a case of IBS accompanied by anxiety and a depressive state. Patient consent for this report was obtained.

Case

The patient was a 52-year-old housewife. She had no history of mental illness and lived with her husband. She had been visiting a nearby physician for treatment of IBS with predominant diarrhea, and she was taking a lactobacillus preparation. She received a preoperative psychiatry consultation after being informed of a diagnosis of ovarian cancer, because anxiety, depressed mood, and insomnia were observed, in addition to her existing diarrhea and abdominal pain.

At the time of her examination, her facial expression was haggard, and she was fidgeting and acting restless. Feelings of depressed mood, anxiety, and irritability, as well as difficulty falling asleep were observed. However, decreased motivation and loss of appetite were not observed. Based on these symptoms, she was diagnosed with adjustment disorder (mixed depressed mood and anxiety type) based on the DSM-IV-TR[5]. She scored 22 points on the Hamilton Rating Scale for Depression (HAM-D)[6], and 28 points on the Hamilton Rating Scale for Anxiety (HAM-A)[7]. The HAM-D consists of 17 items and is still widely used today to measure the severity of a patient's major depression in both clinical and research settings. The HAM-A consists of 14 items and is still widely used today to measure the severity of anxiety

Correspondence to Katsunaka Mikami, Department of Psychiatry, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa 259–1143, Japan
E-mail: mikami@is.icc.u-tokai.ac.jp
Journal Website (http://www2.nms.ac.jp/jnms/)

symptoms in both clinical and research settings.

MIR 15 mg/day was started to target her IBS and adjustment disorder with anxiety and depressed mood. Doctors within the department of gastroenterological surgery administered medications including lactobacillus, polycarbophil calcium, scopolamine butylbromide, and loperamide for the IBS. However, the effect on the abdominal pain and diarrhea was minimal. Her stool frequency was at, or above, 10 times per day. She was unable to go out due to anxiety about diarrhea. After two weeks, the MIR dosage was increased to 30 mg/day. A gradual improvement in anxiety, irritability, and depressed mood was observed. After one month, signs of improvement in abdominal pain and diarrhea were also apparent, and her stool frequency had decreased to approximately 3 to 5 times per day. At this time, her HAM-D score was 5 points and her HAM-A score was 11 points. After two months, in addition to the anxiety and depressive state, improvements were observed in her diarrhea and abdominal pain, and her stool frequency was 3 times per day or less. She was able to do housework and go out. After this, MIR was gradually decreased, and a recurrence of the psychiatric or IBS symptoms was not observed. She currently continues her outpatient hospital visits and her course is favorable.

Discussion

There are only two previous case reports that investigate the effectiveness of MIR on IBS with comorbid mental illness. The first covered the therapeutic effects of IBS complicated by depression[8] and the second covered the therapeutic effects in a case of IBS with anxiety symptoms[9]. Both studies demonstrated antidepressant effects and therapeutic effects on IBS symptoms, such as abdominal pain and abnormal bowel movements. The woman in the present case presented with anxiety and symptoms of depression due to the distress of being ill, as well as marked diarrhea due to IBS. The patient in this case exhibited symptoms of IBS with predominant diarrhea, and therapies for IBS such as lactobacillus preparations were ineffective. MIR was effective against symptoms of IBS with predominant diarrhea for which treatments such as lactobacillus preparations were ineffective, and it was effective in improving symptoms of depression and anxiety due to the distress of being ill.

The pharmacological action of MIR increases the release of serotonin (5-HT) and noradrenaline within the brain. Further, by antagonizing 5-HT_2 and 5-HT_3 receptors, MIR selectively enhances stimulation of 5-HT_{1A} receptors. Therefore, MIR has both antidepressant and antianxiety effects[10]. 5-HT_3 receptors regulate peristaltic movement in the alimentary canal and have an effect on stool formation and gastrointestinal transit time. In IBS with predominant diarrhea in particular, the 5-HT_3 receptors are stimulated excessively, and peristaltic movement in the alimentary canal is exacerbated. The gastrointestinal transit time is reduced accordingly, the digestive tract cannot absorb moisture sufficiently, and diarrhea occurs. Further, 5-HT_3 receptors facilitate the transmission of pain sensation in the colon and abdominal pain and visceral hypersensitivity are exhibited. MIR has been shown to antagonize 5-HT_3 receptors, a unique factor among antidepressants. The 5-HT_3 antagonism of MIR can improve the abnormal bowel movements accompanying exacerbated alimentary canal movements, as well as suppress the transmission of pain in the colon. This can be expected to improve abdominal pain and visceral hypersensitivity. As a result, it is thought that the 5-HT_3 antagonism of MIR can be more effective in treating IBS with predominant diarrhea. In the present case, with the use of MIR, the patient demonstrated improvement in anxiety, irritability, and depressed mood; lessened abdominal pain and diarrhea; and a decreased stool frequency.

Dysregulation of neurotransmitters in the brain-gut interaction has been found to be one cause of IBS[11]. Approximately 95% of 5-HT exists in the enteric nervous system (ENS); of this, 90% is contained in enterochromaffin (EC) cells, and the remainder exists in ENS neurons. The primary 5-HT receptors in the digestive tract are 5-HT_3, 5-HT_4, and 5-HT_{1b} receptors. The 5-HT_3 receptors in particular transmit pain signals from the intestines to the brain when an external sensory neuron is stimulated. The 5-HT_3 receptor is stimulated by 5-HT released from EC cells and, as a result, nausea or a feeling of abdominal bloating may occur[12]. Through its antagonistic effect on 5-HT_3 receptors, the MIR used in this study improved exacerbated gastrointestinal movement, as well as abnormal bowel movements, such as diarrhea. Furthermore, abdominal pain and visceral hypersensitivity were improved by suppressing the transmission of pain in the colon. In other words, MIR led to improvement in the diarrhea and pain associated with IBS with predominant diarrhea. In times of psychosocial stress, movement of the digestive tract is provoked via the parasympathetic nervous system, and permeability of the intestinal mucosa is exacerbated, leading to visceral hypersensitivity. These cause abdominal pain and abnormal bowel move-

ments to occur, as well as changes in intestinal flora. Due to these changes, visceral hypersensitivity is further heightened, and excitation sensitivity of the central nervous system is exacerbated via afferent pathways. This concept is known as brain-gut interaction. In the brains of patients with IBS, the amygdala, anterior cingulate gyrus, and insula-which control the stress response-become overactive, triggering anxiety and depression. These symptoms of anxiety and depression further worsen IBS symptoms, causing a vicious cycle[13]. In this case, the patient's depressed mood, anxiety, and irritability increased due to the distress of being ill, further worsening her IBS symptoms of diarrhea and abdominal pain. Even when medications such as high molecular weight polymer and anticholinergic or antidiarrheal drugs were used, the diarrhea and abdominal pain remained severe. The worsening of the IBS symptoms was linked to further worsening of her depressed mood and symptoms of anxiety, demonstrating the brain-gut interaction. MIR improved the patient's mood and symptoms of anxiety, which remained even after completion of the cancer treatment, and it also improved the symptoms of IBS. Its therapeutic effect broke the cycle of depressed mood, anxiety, and symptoms of IBS, causing an improvement in the symptoms of IBS as well as in the patient's mood. In this case, MIR contributed to the improvement of abdominal symptoms and psychiatric symptoms via the brain-gut interaction.

Ramosetron hydrochloride, a 5-HT_3 receptor antagonist drug, is used in patients with IBS with predominant diarrhea. In Japan, ramosetron hydrochloride was initially said to be appropriate only for men but, recently, usage in women has gradually increased. For women, the dosage of ramosetron hydrochloride is set at half the dose for men, and more careful administration is necessary. Antidepressant drugs such as selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, and selective noradrenaline reuptake inhibitors(SNRIs) improve abnormalities in visceral sensation, thereby improving symptoms of IBS such as abdominal pain. However, antidepressant drugs stimulate 5-HT_3 receptors, and it is possible that nausea and abnormal bowel movements may worsen as a side effect. On the other hand, MIR, unique among antidepressants, produces a 5-HT_3 receptor antagonist effect. It can be expected that the therapeutic effects will be similar to those of the 5-HT_3 receptor antagonist drug ramosetron hydrochloride. Accordingly, it is thought that MIR could be particularly effective for patients suffering from IBS with predominant diarrhea. Among the types of IBS, IBS with predominant diarrhea causes the greatest dysfunction in one's social life. In the present case, the patient had difficulty going out due to anxiety about diarrhea, and a great impairment in her social life was observed.

In this study, the 5-HT_3 receptor antagonist action of MIR improved the abnormal bowel movements that accompany exacerbated alimentary canal movement. Transmission of pain in the colon was suppressed, resulting in improvement in abdominal pain and visceral hypersensitivity. The study therefore suggests that MIR is particularly effective in treating IBS with predominant diarrhea. This case report suggests the efficacy of MIR for both psychiatric and abdominal symptoms (via the brain-gut interaction) for the treatment of IBS with predominant diarrhea accompanied by depression and anxiety.

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References

1. Mearin F, Lacy BE, Chang L, Chey WD, Lembo AJ, Simren M, Spiller R: Bowel Disorders. Gastroenterology 2016.
2. Lovell RM, Ford AC: Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. Clin Gastroenterol Hepatol 2012; 10: 712–721.e4.
3. Drossman DA, McKee DC, Sandler RS, Mitchell CM, Cramer EM, Lowman BC, Burger AL: Psychosocial factors in the irritable bowel syndrome. A multivariate study of patients and nonpatients with irritable bowel syndrome. Gastroenterology 1988; 95: 701–708.
4. Garakani A, Win T, Virk S, Gupta S, Kaplan D, Masand PS: Comorbidity of irritable bowel syndrome in psychiatric patients: a review. Am J Ther 2003; 10: 61–67.
5. American Psychiatric Association: Diagnostic and Statisical Manual of Mental Disorder, Fourth Edition Text Revision. APA, editor. Washington, D.C. 2000.
6. Hamilton M: A rating scale for depression. Journal of neurology, neurosurgery, and psychiatry 1960; 23: 56–62.
7. Hamilton M: The assessment of anxiety states by rating. The British journal of medical psychology 1959; 32: 50–55.
8. Thomas SG: Irritable bowel syndrome and mirtazapine. Am J Psychiatry 2000; 157: 1341–1342.
9. Spiegel DR, Kolb R: Treatment of irritable bowel syndrome with comorbid anxiety symptoms with mirtazapine. Clin Neuropharmacol 2011; 34: 36–38.
10. Holm KJ, Markham A: Mirtazapine: a review of its use in major depression. Drugs 1999; 57: 607–631.
11. Mach T: The brain-gut axis in irritable bowel syndrome--clinical aspects. Med Sci Monit 2004; 10: Ra125–131.
12. Camilleri M: Serotonergic modulation of visceral sensation: lower gut. Gut 2002; 51 (Suppl 1): i81–86.
13. Drossman DA, Hasler WL: Rome IV-Functional GI Disorders: Disorders of Gut-Brain Interaction. Gastroenterology 2016; 150: 1257–1261.

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