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# Efficacy of Acotiamide in Combination with Esomeprazole for Functional Dyspepsia Refractory to Proton-Pump Inhibitor Monotherapy

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Functional dyspepsia (FD) is a gastroduodenal disorder that presents as postprandial fullness, early satiation, or epigastric burning despite no evidence of a structural disease. Proton pump inhibitors (PPIs) are often the first choice for treating FD. However, some patients need additional medication because of residual symptoms despite a certain level of benefit from the PPI. For these patients, a combination of PPI and other agents has a possibly more beneficial effect than changing their medication. This study aimed to evaluate the efficacy of an initial PPI followed by combination therapy with PPI and acotiamide in FD patients with residual symptoms after an initial PPI. We enrolled 105 patients who started an initial PPI (20 mg of esomeprazole once a day). Twenty-three patients with residual symptoms received 100 mg of acotiamide, a cholinesterase inhibitor, three times a day with esomeprazole as a combination therapy for 2 weeks. The symptoms were evaluated using the modified Frequency Scale for the Symptoms of Gastroesophageal Reflux Disease (mFSSG). Eighteen of 23 patients (78%) achieved an overall improvement in symptoms. Almost all FD-related symptoms statistically improved after the combination therapy, with an improvement in the mFSSG score relevant to the postprandial distress syndrome and epigastric pain syndrome. The symptoms improved regardless of age, sex, and the pre-combination therapy score of the mFSSG. Our findings suggest that the combination therapy of acotiamide and PPI may be effective in selected FD patients with insufficient improvement with an initial PPI. However, well-designed trials are required to confirm the efficacy.

**Keywords:** acotiamide; esomeprazole; functional dyspepsia; prokinetic agent; proton pump inhibitor
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## Introduction

Functional dyspepsia (FD) is a gastroduodenal disorder that presents as postprandial fullness, early satiation, or epigastric burning despite no evidence of a structural disease that is likely to explain the symptoms for over 6 months (Drossman 2006). Prolonged dyspepsia symptoms cause a noticeable deterioration of quality of life (QOL). Various therapies such as administration of proton pump inhibitors (PPIs), histamine-type 2 receptor antagonists, or prokinetic agents or eradication of *Helicobacter pylori* have been used as treatment for FD (Lacy et al. 2012). PPIs are often the first choice of treatment for FD. However, the efficacy of PPIs in patients with FD is limited and may be confined to those patients who have reflux-like or ulcer-like dyspepsia (Wang et al. 2007). In clinical practice, a medication change is considered when there is no improvement in FD symptoms after PPI therapy. However, some patients need additional agents despite a certain level of benefit from a PPI, especially patients with severe symptoms. For these patients, a combination of PPI and other agents with different mechanisms of action may exert a more beneficial effect than a medication change from a PPI to another agent.

Acotiamide, a cholinesterase inhibitor, is a novel gastroprokinetic agent that is different from traditional prokinetic agents, which act on a serotonin or dopaminergic receptor. Moreover, acotiamide has an inhibitory effect on the muscarinic receptor, and it causes inhibition by suppressing feedback to the acetylcholine release. In a multicenter, randomized, placebo-controlled trial of 892 Japanese FD patients, the efficacy of 100 mg of acotiamide three

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times a day was compared to that of a placebo for 4 weeks (Matsueda et al. 2012). The study demonstrated improvement in global assessment of overall treatment efficacy and the elimination of meal-related symptoms.

To the best of our knowledge, it has not been determined whether the combination therapy with acotiamide and PPI is effective in patients with FD. Therefore, we have hypothesized that acotiamide in combination with a PPI is effective in FD patients with residual symptoms despite a certain level of benefit achieved with an initial PPI. We report the results of a pilot study in 23 patients with FD refractory to initial PPI monotherapy that were subsequently treated with PPI and acotiamide as combination therapy.

## Methods

From June 2013 to December 2013, we enrolled 105 patients who were newly diagnosed with FD and met the criteria for Rome III according to the physicians' history taking and esophagogastroduodenoscopy performed at the Oizumichuo Clinic (Tokyo, Japan). As an initial treatment, we administered a PPI for at least one week (20 mg of esomeprazole once a day). After the initial PPI, we obtained a careful history and excluded 82 patients who experienced remission of their symptoms or deemed the initial PPI totally ineffective. Then, we enrolled 23 patients with an insufficient level of improvement despite a certain level of effects achieved with the initial PPI. These patients with residual symptoms received an additional acotiamide (100 mg) three times a day with esomeprazole as combination therapy for 2 weeks. We assessed the intensity of their symptoms by using the modified Frequency Scale for the Symptoms of Gastroesophageal Reflux Disease (mFSSG) (Kusano et al. 2012) before treatment, after the initial PPI, and at 2 weeks after the addition of acotiamide. The study was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments. We obtained informed consent from all patients.

*Statistical analyses*

Statistical analyses were performed using SPSS, version 21 statistical software (IBM Corp., Armonk, NY, USA). Clinical variables were analyzed using Student's *t*-test. Differences were considered statistically significant at $p < 0.05$.

## Results

The mean age of the patients was 56.4 years (6 male and 17 female). The changes in the mFSSG score before treatment and after the initial PPI therapy are shown in Table 1. The scores of the mFSSG showed a tendency to improve after the initial PPI; however, this was not statistically significant. After 2-week administration of acotiamide and PPI (esomeprazole), the treatment was completed in all 23 patients. Eighteen of 23 patients (78%) showed improvement in symptoms. There were no severe adverse events; however, metrorrhagia and breast pain occurred as side effects from the treatment in one female patient. The data regarding symptoms before and after combination therapy assessed with the mFSSG are shown in Fig. 1. Most symptoms statistically improved after the administration of PPI and the acotiamide combination therapy, except in one question related to gastroesophageal reflux disease (GERD): "Do you sometimes subconsciously rub your chest with your hand?" However, the mFSSG scores of the other 6 out of 7 questions relevant to GERD were improved. There was improvement in the mFSSG total score relevant to both GERD and dyspepsia (Table 2). Furthermore, the combination therapy with acotiamide and PPI improved the mFSSG score regardless of age, sex, and the pre-treatment score of the mFSSG.

## Discussion

To the best of our knowledge, the present study is the first report to evaluate the efficacy of acotiamide and PPI as combination therapy for FD. The combination therapy with acotiamide and PPI provided statistically significant improvements in the symptoms of FD.

Based on a presumed relationship between the symptom patterns and the underlying pathophysiological mechanisms, the Rome III criteria categorize FD further as postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS). Although a standard treatment for FD has not been established, PPIs are widely used as the initial treatment choice in patients with EPS dominant FD. Several randomized controlled studies suggested that the efficacy of PPI therapy for FD is limited, and it may be confined to those patients who have co-existing EPS (Talley et al. 1998; Blum et al. 2000; Bolling-Sternevald et al. 2002; Wong et al. 2002; Peura et al. 2004). One randomized control study compared PPI therapy to a placebo in FD patients with ulcer-like symptoms (van Rensburg et al. 2008). In their selected patient population, PPI therapy had a modest but statistically significant advantage over the placebo. Furthermore, van Zanten et al. (2006) reported that

Table 1. Changes in the modified Frequency Scale for the Symptoms of Gastroesophageal Reflux Disease (mFSSG) score before treatment and after initial PPI therapy.

| | Pre-treatment | Post-initial PPI | *p*-value |
|---|---|---|---|
| Points of mFSSG, mean ± S.D. ($n = 23$) | | | |
| GERD score | 10.6 ± 6.1 | 8.5 ± 6.6 | 0.442 |
| Dyspepsia score | 14.6 ± 7.3 | 10.6 ± 6.1 | 0.164 |
| Total score | 25.1 ± 12.8 | 19.1 ± 11.4 | 0.196 |

GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor; SD, standard deviation.

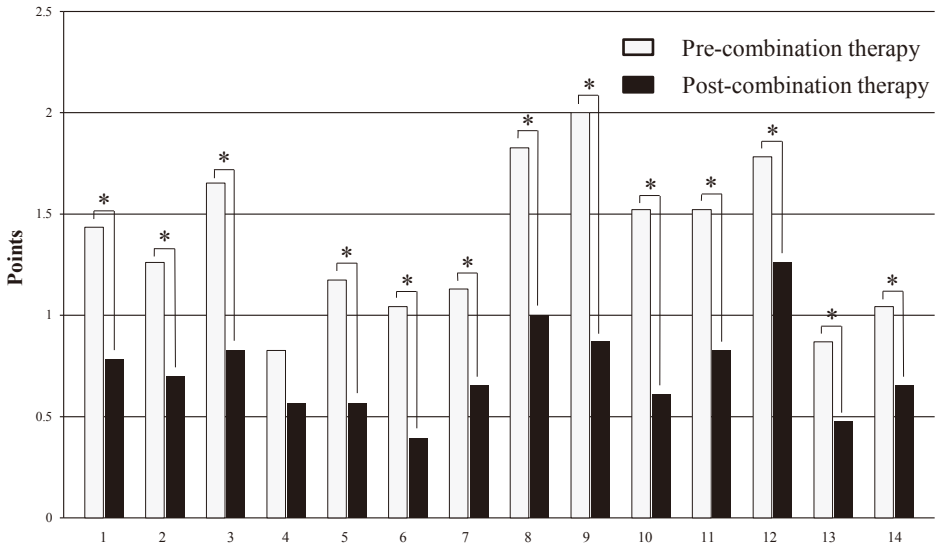


Fig. 1. Changes in patients' symptoms before and after combination therapy.
Changes in patients' symptoms before and after combination therapy with a proton pump inhibitor (PPI) and acotiamide, as assessed using the modified Frequency Scale for the Symptoms of Gastroesophageal Reflux Disease (mFSSG). The symptoms statistically improved after the administration of combination therapy, except according to one question in the mFSSG related to gastroesophageal reflux disease. *$p$-value < 0.05.

Table 2. Changes in the modified Frequency Scale for the Symptoms of Gastroesophageal Reflux Disease (mFSSG) score before and after combination therapy with a PPI and acotiamide.

| | Pre-combination therapy | Post-combination therapy | $p$-value |
|---|---|---|---|
| Points of mFSSG, mean ± S.D. ($n$ = 23) | | | |
| GERD score | 8.5 ± 6.6 | 4.4 ± 5.2 | 0.002 |
| Dyspepsia score | 10.6 ± 6.1 | 5.7 ± 5.0 | < 0.001 |
| Total score | 19.1 ± 11.4 | 10.2 ± 9.4 | < 0.001 |
| Total score of mFSSG by category, mean ± S.D. | | | |
| Male ($n$ = 6) | 15.7 ± 13.8 | 5.3 ± 6.9 | 0.026 |
| Female ($n$ = 17) | 20.3 ± 10.6 | 11.9 ± 9.8 | < 0.001 |
| Age ≤ 50 y ($n$ = 12) | 20.7 ± 13.1 | 11.5 ± 10.4 | 0.005 |
| Age > 50 y ($n$ = 11) | 17.6 ± 10.0 | 8.9 ± 8.7 | 0.002 |
| Dyspepsia dominant ($n$ = 16) | 19.9 ± 13.3 | 11.3 ± 10.5 | 0.001 |
| GERD dominant ($n$ = 7) | 17.3 ± 5.4 | 7.5 ± 6.5 | 0.005 |
| Total points ≤ 19 ($n$ = 14) | 11.4 ± 4.0 | 4.8 ± 4.6 | < 0.001 |
| Total points > 20 ($n$ = 9) | 31.1 ± 8.0 | 18.4 ± 9.2 | 0.006 |

GERD, gastroesophageal reflux disease; S.D., standard deviation.

there was no statistically significant difference between high-dose PPI therapy (esomeprazole, 40 mg a day) and a placebo in patients with FD. These studies revealed that potent inhibition of acid secretion had a limited role in the treatment of FD. In contrast, acotiamide is a gastrointestinal motility modulator, with a different functional mechanism compared to PPIs. It exhibits little affinity for serotonin 5-$HT_2$, 5-$HT_3$, and 5-$HT_4$ receptors and a weak affinity for dopamine D2 receptors; however, it exhibits a strong affinity for muscarinic M1/M2 receptors (Nakajima et al. 2000; Ogishima et al. 2000). It exerts gastroprokinetic activity by inhibiting acetylcholinesterase activity and enhancing the release of acetylcholine via its antagonistic actions on the muscarinic receptors. In a rat model, DNA microarray analysis showed that the expression levels of stress-related genes such as the $\gamma$-aminobutyric acid (GABA) receptors, GABA transporters, and neuromedin U in the medulla oblongata or hypothalamus were altered

after the administration of acotiamide (Seto et al. 2008). Additionally, a large-scale randomized controlled study revealed that acotiamide was better than a placebo in improving the overall treatment efficacy of PDS, particularly with regard to postprandial fullness, upper abdominal bloating, and early satiation (Matsueda et al. 2012). It may be difficult to improve both PDS and EPS symptoms by using single agent therapy because of the complexity of FD. However, a synergetic effect between acotiamide and PPI therapy may have a different pharmacological function that would improve FD-related symptoms.

Limitations of this study were the small size, single center, no placebo-controlled group, and the short treatment duration of only 2 weeks. In this study, the initial PPI followed by combination therapy with a PPI and acotiamide was effective in selected patients with insufficient improvement despite a certain level of effects with the initial PPI. Nevertheless, well-designed, multicenter, placebo-controlled, prospective trials are required to confirm the efficacy of this finding. We believe that an initial PPI followed by combination therapy with acotiamide is an option in patients with FD refractory to PPI.

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## Conflict of Interest

The authors declare no conflict of interest.

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