# Effective Combination Therapy with Nizatidine and Acotiamide for Functional Dyspepsia

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## ABSTRACT

***Background:*** *The two subgroups of functional dyspepsia (FD), including postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS), can overlap. PDS–EPS overlap tends to reduce patients' quality of life. Combination therapy with nizatidine and acotiamide may improve the symptoms of FD, including PDS–EPS overlap. A previous study reported the combined effect of rabeprazole and acotiamide. This study aimed to evaluate nizatidine as an alternative to rabeprazole.*

***Methods:*** *This single-center retrospective study analyzed 66 patients with FD, including 45 and 21 patients receiving nizatidine/acotiamide and rabeprazole/acotiamide therapies, respectively. The regimen comprised nizatidine 150 mg twice daily, rabeprazole 10 mg once daily, and acotiamide 100 mg thrice daily. No prokinetics other than acotiamide (e.g., rikkunshito and mosapride) were simultaneously administered. The following characteristics were investigated: age, sex, diabetes mellitus, Parkinson's disease, mental illness, subgroups of FD (PDS, EPS, or PDS–EPS overlap), and treatment-emergent adverse events. Symptom improvement rates following treatment were calculated and compared.*

***Results:*** *Although differences in the FD subgroups were significant in terms of patients' backgrounds, no significant difference in PDS–EPS overlap rates was observed (55.6% [25/45] vs. 61.9% [13/21], p = 0.79). The difference in symptom improvement rates between nizatidine/acotiamide and rabeprazole/acotiamide therapies was not significant (86.7% [39/45] vs. 85.7% [18/21], p = 1).*

***Conclusion:*** *Nizatidine/acotiamide therapy demonstrated efficacy comparable to rabeprazole/acotiamide therapy in treating FD. Patients with FD frequently experience treatment difficulties owing to various underlying factors; however, nizatidine/acotiamide therapy with a high symptom improvement rate is a promising therapeutic option in refractory FD.*

***Keywords:*** *Dyspepsia, nizatidine, rabeprazole*

## ABSTRAK

***Latar belakang:*** *Dua subkelompok Functional Dyspepsia (FD), yaitu Postprandial Distress Syndrome (PDS) dan Epigastric Pain Syndrome (EPS), dapat saling overlap. Overlap PDS-EPS dapat menurunkan kualitas hidup pasien. Terapi kombinasi dengan nizatidine dan acotiamide dapat memperbaiki gejala-gejala FD, termasuk overlap PDS-EPS. Penelitian sebelumnya melaporkan efek kombinasi rabeprazole dan acotiamide. Penelitian ini bertujuan untuk mengevaluasi nizatidine sebagai alternatif untuk rabeprazole.*

***Metode:*** *Penelitian retrospektif ini menganalisis 66 pasien dengan FD, termasuk 45 pasien menerima terapi nizatidine/acotiamide dan 21 pasien menerima rabeprazole/acotiamide. Regimen yang diberikan adalah nizatidine 150 mg dua kali sehari, rabeprazole 10 mg sekali sehari, dan acotiamide 100 mg tiga kali sehari.*

*Tidak ada prokinetik selain acotiamide (misalnya, rikkunshito dan mosapride) yang diberikan secara bersamaan. Karakteristik yang dinilai adalah: usia, jenis kelamin, diabetes mellitus, penyakit Parkinson, penyakit mental, subkelompok FD (PDS, EPS, atau overlap PDS-EPS), dan efek samping yang muncul setelah pengobatan. Tingkat perbaikan gejala setelah pengobatan dinilai dan dibandingkan.*

***Hasil:*** *Terdapat perbedaan yang bermakna pada karakteristik dasar pasien, namun tidak ada perbedaan yang bermakna pada kejadian overlap PDS-EPS (55,6% [25/45] vs 61,9% [13/21], p = 0,79). Tidak terdapat perbedaan yang bermakna pada tingkat perbaikan gejala antara yang diberikan nizatidine/acotiamide dan rabeprazole/acotiamide (86,7% [39/45] vs 85,7% [18/21], p = 1).*

***Kesimpulan:*** *Terapi nizatidine/acotiamide menunjukkan efektivitas yang setara dengan terapi rabeprazole/acotiamide dalam mengobati FD. Pasien dengan FD sering mengalami kesulitan pengobatan karena berbagai faktor yang mendasari; Namun, terapi nizatidine / acotiamide dengan tingkat perbaikan gejala yang tinggi merupakan pilihan terapi yang menjanjikan pada FD refrakter.*

***Kata kunci:*** *Dispepsia, nizatidine, rabeprazole*

## INTRODUCTION

According to the Rome criteria, functional dyspepsia (FD) is divided into the following two subgroups: postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS). However, PDS and EPS can overlap, with a prevalence rate of approximately 20% in both Japan and Western countries.[1,2] Furthermore, PDS–EPS overlap more frequently reduces the quality of life than PDS or EPS.[2]

The Japanese guideline recommends proton pump inhibitors (PPIs), acotiamide, and Japanese herbal medicine (rikkunshito) as the first-line therapy for FD.[3] In particular, acotiamide was first approved for FD in Japan.[4] Acotiamide was developed on the basis of the anti-acetylcholine esterase activity, the mechanism that increases gastric motility in nizatidine; however, acotiamide has no antisecretory effects.[5] Therefore, combination therapy with acotiamide and nizatidine, a histamine-2 receptor antagonist (H2RA), may improve the symptoms of FD, including PDS–EPS overlap, by the additional antisecretory effect and further increased gastric emptying. A previous study reported that combination therapy with acotiamide and rabeprazole, a PPI, was more effective than monotherapy in patients with FD from Japan.[6] The present study compared the combined effect of nizatidine and acotiamide with that of rabeprazole and acotiamide.

## METHODS

This retrospective study included 83 patients with FD from Japan who received combination therapy with nizatidine and acotiamide or rabeprazole and acotiamide in Fuyoukai Murakami Hospital from October 1, 2014 to September 30, 2024. The following patients were excluded from this study: eight and nine patients with unknown outcome and *Helicobacter pylori* infection, respectively. Finally, 66 patients were analyzed. In this study, FD was defined as "a condition chronically presenting symptoms centered in the upper abdomen, including epigastric pain or discomfort, in the absence of any organic, systemic, or metabolic disease that is likely to explain the symptoms," as stated by the Japanese guideline.[3] Most patients in Japan do not meet the Rome criteria because they visit a medical facility with a short symptom duration.[7,8] The regimen comprised nizatidine 150 mg twice daily, rabeprazole 10 mg once daily, and acotiamide 100 mg thrice daily. No prokinetics other than acotiamides (e.g., rikkunshito and mosapride) were simultaneously administered.

The following characteristics extracted from the medical records were investigated: age, sex, diabetes mellitus, Parkinson's disease, mental illness, subgroups of FD (PDS, EPS, or PDS–EPS overlap), and treatment-emergent adverse events. Symptom improvement rates following treatment were calculated. To identify significant differences between the two groups, the Mann–Whitney U test or Fisher's exact test was used. Statistical analysis was performed using EZR (Easy R, Version 1.68),[9] and *p*-values of $<0.05$ were considered statistically significant. This study was approved by the Institutional Ethics Committee (UMIN-CTR issued approval UMIN000056721), and patients provided informed consent.

## RESULTS

The patients' backgrounds are summarized in **Table 1**. The majority of the patients were female, and none of the patients with Parkinson's disease were included in the study. Among the six patients with

diabetes mellitus, only one had a hemoglobin A1c of >8.0%, indicating poor control. No adverse events were reported.

No significant differences were observed except in the FD subgroups. The difference in symptom improvement rates between nizatidine/acotiamide and rabeprazole/acotiamide therapies was not significant in **Figure 1.**

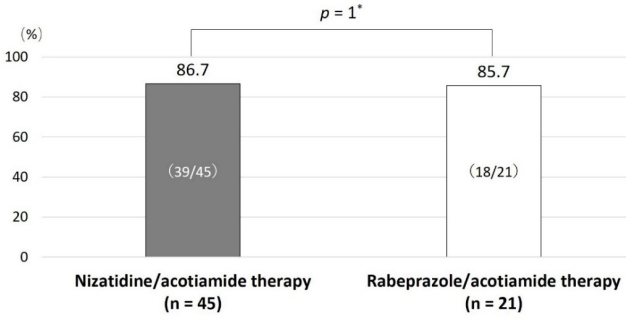
**Table 1. Patients' backgrounds**

| | Nizatidine/ acotiamide therapy (n = 45) | Rabeprazole/ acotiamide therapy (n = 21) | *p*-value |
|---|---|---|---|
| Male, n (%) | 15 (33.3) | 5 (23.8) | 0.569* |
| Age, years (range) | 57 (21–83) | 61 (17–79) | 0.847† |
| Diabetes mellitus‡, n (%) | 3 (6.7) | 3 (14.3) | 0.373* |
| Parkinson's disease, n (%) | 0 | 0 | 1* |
| Mental illness, n (%) | 9 (20.0) | 7 (33.3) | 0.355* |
| Subgroups | | | 0.000819* |
| PDS, n (%) | 19 (42.2) | 2 (9.5) | |
| EPS, n (%) | 1 (2.2) | 6 (28.6) | |
| PDS-EPS overlap, n (%) | 25 (55.6) | 13 (61.9) | |
| Adverse events, n (%) | 0 | 0 | 1* |

*: Fisher's exact test.

†: Mann–Whitney U test.

‡: One patient has a hemoglobin A1c of >8.0% (poor control) in the rabeprazole/ acotiamide therapy group.




*: Fisher's exact test.

**Figure 1. Symptom improvement rates following treatment**

## DISCUSSION

This study showed that the effect of nizatidine/ acotiamide therapy was high similar to that of rabeprazole/acotiamide therapy in Japanese patients with FD. A randomized double-blind study reported that famotidine, an H2RA, showed no add-on effects on FD.[10] The reason is likely because famotidine never affects gastric motility.[11-14] Conversely, rabeprazole decreases gastric emptying in Japanese participants.[15-19] As gastric acid causes symptoms of PDS in patients with FD and healthy participants,[20-21] the benefits of PPIs due to their potent antisecretory effect may exceed the decreased gastric emptying-associated disadvantages.

However, a stronger antisecretory effect does not inherently translate to superior therapeutic outcomes. A systematic review of the therapeutic efficacy for FD has revealed that the standard dose of PPIs is superior to the high dose of PPIs in the resolution and improvement of symptoms, and PPIs are inferior to H2RAs in symptomatic improvement.[22] Nizatidine has been reported to significantly improve the symptoms of PDS and EPS owing to increased gastric motility in Japanese patients with FD with impaired gastric emptying.[23] Up to 40% of patients with FD have delayed gastric emptying.[24] Thus, gastric emptying is a significant factor for FD. The results of this study suggest that a high antisecretory activity, including PPIs, is not necessary in acotiamide combined therapy when the antisecretory drug increases gastric emptying.

This study had several limitations. First, the sample size was small, and the study design was a single-center retrospective study without crossover. Second, the difference in the FD subgroups was significant in terms of patients' backgrounds. However, no significant differences in PDS–EPS overlap rates were noted (nizatidine/acotiamide therapy [55.6%] vs. rabeprazole/ acotiamide therapy [61.9%], $p = 0.79$). Furthermore, a study conducted in Japan reported that the evaluation of pathophysiology by the classification of subgroups had insufficient evidence in Japanese patients with FD.[25] Consequently, subgroup variations likely had minimal impact on the study outcomes. Patients with FD frequently encounter treatment difficulties owing to various underlying factors. Nizatidine/acotiamide therapy, showing a high symptom improvement rate, is a promising therapeutic option in refractory FD.

## CONCLUSION

Combination therapy with nizatidine and acotiamide therapy demonstrated efficacy comparable to rabeprazole and acotiamide therapy in treating FD.

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