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Extensive gastric mucosal atrophy is a possible predictor of clinical effectiveness of acotiamide in patients with functional dyspepsia

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Key words
acotiamide – gastric mucosal atrophy – mental disorder

Abstract. Background: Acotiamide is known as an effective agent for functional dyspepsia. However, clinical factors related to its effectiveness have not been fully elucidated, so it is difficult to predict the drug's effectiveness prior to its administration in patients. Aims: The present retrospective study was conducted to examine the relationship between clinical factors and the effectiveness of acotiamide for functional dyspepsia. Materials and methods: The study subjects were 149 patients with functional dyspepsia who were prescribed acotiamide. Based on medical records and clinical factors, including endoscopic findings, the effectiveness of acotiamide was investigated. Results: Significant clinical factors associated with acotiamide's effectiveness were identified. These included postprandial syndrome, concomitant mental disorder, and extensive gastric mucosal atrophy. On multiple regression analysis, extensive gastric mucosal atrophy showed the strongest relationship with the clinical effectiveness of acotiamide; the other significant factor was concomitant mental disorder. Conclusion: Although the pathophysiology of the relationship between mucosal atrophy and acotiamide remains uncertain, a decrease in hormonal secretion, such as that of ghrelin, may be a possible mechanism.

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Introduction

Functional dyspepsia (FD) is a common disorder of the upper gastrointestinal tract that is frequently accompanied by epigastric discomfort, fullness, or pain. The number of patients experiencing FD is estimated to be up to one fourth of the population in the United States, and FD is known to impair health-related quality of life [1]. Acotiamide is a selective acetylcholinesterase inhibitor developed as an agent useful in the treatment of FD. In meta-analysis, the efficacy of acotiamide has been proven to significantly surpass the effect of placebo [2]. With its clinical effectiveness reaching as high as 53%, acotiamide seems to be more efficacious for postprandial distress syndrome than for epigastric pain syndrome [3, 4]. However, it is difficult for clinicians to predict the effectiveness of acotiamide prior to its administration because factors associated with its effectiveness have not been elucidated. In Japan, although esophagogastroduodenoscopy (EGD) before initiation of acotiamide is required, the usefulness of endoscopic findings for the prediction of acotiamide's effectiveness remains unclear. This retrospective study was conducted to clarify clinical factors related to the effectiveness of acotiamide, including endoscopic findings.

Materials and methods

This was a retrospective study analyzing the medical records of patients at Teikyo University Hospital (Tokyo, Japan). At first, all 212 patients who had been prescribed acotiamide (Acofide® tablets 100 mg, Zeria Pharmaceutical Co., Ltd., Tokyo, Japan) 100 mg t.i.d. for FD in the Department of Internal Medicine from January 2014 through December 2015 were identified from patient lists. 63 patients whose response to acotiamide could not be determined due to insufficient description or lack of follow-up were excluded from the study, and at the end

Table 1. Clinical factors and their relationship with the effectiveness of acotiamide.

Factors		Crude OR	95% CI	p-value
Age (mean ± SD, years)	58.5 ± 18.6	0.996	0.974 – 1.018	0.687
Sex (female)	93 (62.4%)	1.050	0.458 – 2.409	0.908
Helicobacter pylori (P/N/Eradicated)	13/19/18	3.310	0.372 – 29.43	0.283
Type of FD				
PDS	120 (80.6%)	4.000	1.638 – 9.768	0.002
EPS	75 (50.4%)	0.430	0.185 – 0.996	0.049
Coexisting disease				
NERD	37 (24.8%)	0.886	0.356 – 2.204	0.795
IBS	17 (11.4%)	2.066	0.445 – 9.597	0.354
Constipation	25 (16.8%)	1.032	0.351 – 3.035	0.954
Mental disorder	27 (18.1%)	0.140	0.056 – 0.352	< 0.001
Concomitant drugs				
Acid suppressants	112 (75.1%)	1.182	0.474 – 2.946	0.720
Prokinetics	55 (36.9%)	0.506	0.225 – 1.139	0.100
Endoscopic finding				
Gastric mucosal atrophy	52 (34.9%)	0.184	0.078 – 0.435	< 0.001
Hiatal hernia	101 (67.8%)	0.458	0.174 – 1.210	0.109
Fundic gland polyp	24 (16.1%)	1.313	0.413 – 4.177	0.644
Hyperplastic polyp	14 (9.4%)	3.557	0.447 – 28.32	0.203

OR = odds ratio, CI = confidence interval; SD = standard deviation; P = positive; N = negative; FD = functional dyspepsia; PDS = postprandial distress syndrome; EPS = epigastric pain syndrome; NERD = non-erosive reflux esophagitis; IBS = irritable bowel syndrome.

149 patients were enrolled. The diagnosis of FD was made according to the Rome III criteria, with symptoms of either early satiety, postprandial fullness three times per week or more, and/or epigastric pain or epigastric burning at least once a week [5]. Medical records of the subjects were examined to judge their responsiveness to acotiamide within 1 month. Responsiveness was categorized by two of the authors (A.M. and T.Y.) as "good" (symptoms had disappeared); "fair" (symptoms had improved but not disappeared); or "no response" (symptoms were unchanged or had worsened). In addition, clinical data, such as demographics, coexistent gastrointestinal or mental diseases possibly influencing the symptoms of FD, concomitant medications, and 4 endoscopic findings (gastric mucosal atrophy, hiatal hernia, hyperplastic polyp, fundic gland polyp), were also reviewed to evaluate the influence on responsiveness. The extent of gastric mucosal atrophy was assessed using the Kimura-Takemoto classification; closed-type mucosal atrophy was diagnosed by an atrophic boundary between the fundic mucosa and the pyloric mucosa located in the antrum or lesser curvature of the gastric body, and open-type mucosal atrophy was diagnosed by an atrophic boundary located in the lateral wall or greater curvature of the gastric body [6].

In the statistical analysis, a p-value < 0.05 was regarded as significant. To clarify significant clinical factors related to responsiveness, univariate and multivariate analysis were performed using logistic regression analysis. All statistical evaluations were performed using SPSS Statistics version 19 (IBM Japan, Tokyo, Japan). This protocol was approved by the Institutional Review Board of Teikyo University prior to the study (TU16-014).

Results

Table 1 shows the background characteristics of the patients. The average age was 58.5 years, and two-thirds of the subjects were female. As a type of FD, postprandial distress syndrome (PDS) was predominant. Regarding coexisting diseases, mental disorders were found in 18% of the subjects. Most of the patients with mental disorders

Table 2. Clinical effectiveness of acotiamide.

Effectiveness	Number of patients	Rate (%)
Good	68	45.6
Fair	51	34.2
No response	30	20.1
Total	149	100

Responsiveness was categorized as "good" (symptoms had disappeared); "fair" (symptoms had improved but not disappeared); or "no response" (symptoms were unchanged or had worsened).

Table 3. Significance of clinical factors in multiple regression analysis.

Factor	Adjusted OR	95%CI	p-value
Gastric mucosal atrophy	0.166	0.061 – 0.452	< 0.001
Mental disorder	0.198	0.066 – 0.594	0.004
PDS	2.935	0.816 – 10.55	0.099
Prokinetics	0.464	0.171 – 1.263	0.133
EPS	0.628	0.189 – 2.088	0.447

OR = odds ratio; CI = confidence interval; PDS = postprandial distress syndrome; EPS = epigastric pain syndrome.

had anxiety disorder, except for 1 patient who had schizophrenia, 1 patient who had bipolar disorder, and 2 patients who had depression. Acid suppressants, mostly proton pump inhibitors, were frequently prescribed concomitantly.

The effectiveness of acotiamide in the present subjects was high, reaching 79.9% (good response, 45.6%; fair response, 34.2%). Nonresponders constituted only 20.1% of the subjects (Table 2). Table 1 shows the subjects' clinical factors and their relationship with the effectiveness of acotiamide (univariate analysis). Significant factors included the type of FD, concomitant mental disorder, and extensive gastric mucosal atrophy. Table 3 shows the result of multiple regression analysis using factors showing p-values < 0.10 in univariate analysis. Significant factors were gastric mucosal atrophy and concomitant mental disorder.

Discussion

The present results show that extensive gastric mucosal atrophy might be related to the clinical effectiveness of acotiamide. Acotiamide increases acetylcholine in the synapses, not only by antagonizing muscarinic receptors, but also by inhibiting acetylcholinesterase activity, which has been proven to enhance postprandial gastric accommodation and gastric emptying in patients with FD. This is the reason why acotiamide is more effective for postprandial distress syndrome than for epigastric pain syndrome [7]. The mechanism is thought to be the enhancement of acetylcholine release from neurons via antagonism against muscarinic receptors [8]. A recent study indicated that the effect of acotiamide is associated with ghrelin concentration [9]. Additionally, Eun Bae et al. [10] reported that ghrelin secretion is decreased in the setting of extensive atrophic gastritis. This information helps postulate an explanation for the present results, i.e., that patients in the present study with extensive gastric mucosal atrophy had significantly less improvement with acotiamide because of a decrease in ghrelin secretion. A further prospective study is required to clarify this hypothesis.

The other significant factor associated with the effectiveness of acotiamide was coexistence of mental disorders including schizophrenia, bipolar disorder, depression, and anxiety disorder. Mental disorders frequently accompany gastrointestinal symptoms, and mental disorders are common in patients with FD [11, 12, 13]. In the present study, acotiamide was less effective in subjects with an accompanying mental disorder. It is known that psychiatric medications are more effective than other medicines for some patients with FD, so we speculate that acotiamide may be less effective for FD patients with mental disorders. However, further study is necessary to prove this conjecture.

Some limitations must be considered in the interpretation of the present data. One is the retrospective study design. A prospective study should be performed to confirm the data obtained here. Second, this study was carried out at a single institution with a small sample size. Multicenter studies need to be conducted in the future.

In conclusion, in the present study, significant clinical factors associated with the effectiveness of acotiamide included postprandial syndrome, concomitant mental disorder, and extensive gastric mucosal atrophy. This finding might be useful for predicting the efficacy of the agent prior to administration.

Funding

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Conflict of interest

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