Effects of Acotiamide on the Esophageal Motility Function in Patients with Esophageal Motility Disorders: A Pilot Study

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Effects of acotiamide on esophageal motility function in patients with esophageal motility disorders: a pilot study

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Abstract

***Background and Aim*:** Acotiamide is a newly developed prokinetic drug that is clinically used to treat functional dyspepsia (FD). The objective of this study was to assess the therapeutic effects of acotiamide in patients with esophageal motility disorders. ***Methods*:** Twenty-nine patients with both symptoms of FD and symptoms suspicious of esophageal motility disorders were enrolled. Esophageal motility function was evaluated by high-resolution manometry before and after 2 weeks administration of acotiamide (100 mg) 3 times per day. ***Results*:** Twenty-nine patients were diagnosed with achalasia (4), esophagogastric junction outflow obstruction (EGJOO) (6), absent peristalsis (2), distal esophageal spasm (4), frequently failed peristalsis (7), weak peristalsis (2) and normal (4). An analysis in all 29 patients showed that acotiamide had no effects on based on distal contractile integral (DCI), basal lower esophageal sphincter (LES) pressure, or integrated relaxation pressure (IRP). Subgroup analysis, however, showed that acotiamide dramatically reduced IRP, from 21.1 ± 2.4 mmHg to 11.5 ± 1.4 mmHg, and DCI, from 3329.7 ± 1054.2 mmHg-cm-s to 2251.7 ± 667.4 mmHg-cm-s, in the six patients with EGJOO. ***Conclusions*:** Acotiamide potentially normalized impaired LES relaxation in patients with EGJOO, while having no effects on normal esophageal motility patterns. Acotiamide may be a promising treatment for EGJOO.

Introduction

Esophageal motility disorders (EMDs) affect coordinated esophageal contractility. EMDs cause difficulty in swallowing, regurgitation of food, and non-cardiac chest pain owing to a lack of coordinated esophageal motility function. High-resolution manometry (HRM) with color pressure topography plots has allowed the evaluation of esophageal motility function more precisely than conventional manometry [1],[2]. Although recent developments in HRM have improved the diagnosis of EMDs, the underlying causes of EMDs have not been identified, thus preventing the determination of fundamental treatments of EMDs. Patients with major EMDs, especially those with achalasia, have severe symptoms, including dysphasia and/or chest pain. These patients require invasive treatment methods, including pneumatic balloon dilation, per-oral endoscopic myotomy (POEM), laparoscopic Heller myotomy and botulinum toxin injection [3-5].

Acotiamide hydrochloride (acotiamide) is a newly developed prokinetic drug that has been approved for the treatment of functional dyspepsia (FD). Acotiamide not only enhanced GI motility in healthy dogs [6] and rats [7], but also improved impaired gastric emptying induced by restraint-stress. Clinically, a phase III trial showed that acotiamide significantly reduced symptom severity and eliminated meal-related symptoms in patients with FD [8]. Acotiamide has been found to improve gastric accommodation, which is impaired in patients with FD [9]. Acotiamide may affect not only the stomach but other GI motility functions. Recent clinical trials have utilized HRM to assess the effects of acotiamide on esophageal motility functions. One study showed that a standard dose of acotiamide did not significantly affected esophageal body peristaltic contractions or lower esophageal sphincter (LES) pressure in healthy volunteers [10]. Another study, however, found that acotiamide reduced the number of transient LES relaxations in healthy subjects. It is therefore unclear whether

acotiamide can improve esophageal motility functions, and its effects on these functions have not yet been examined in patients with EMDs. This study evaluated the effects of acotiamide on esophageal motility functions in patients with symptoms suspicious of EMDs, as determined by HRM.

Methods

Study subjects

FD may overlap with EMDs. This study enrolled 29 patients from Kyushu University Hospital with FD symptoms who also had symptoms suspicious of EMDs, between August 2013 and April 2015. The inclusion criteria were as follows: i) age >20 years; ii) both FD symptoms (abdominal fullness, bloating, and early satiation) and symptoms suggesting EMDs (dysphasia and/or chest pain); and iii) written informed consent obtained. The exclusion criteria were: i) patients who were not candidates for acotiamide treatment; and ii) patients who were judged inappropriate for the study by the attending medical doctors. Acotiamide was administered to treat the FD symptoms, and its effects on EMDs, if any, were also examined. Esophageal motility was assessed by HRM before and after 2 weeks of treatment with acotiamide (100 mg) 3 times per day before meals. Symptom grade was assessed by FSSG score [11]. The study protocol was approved by the Ethics Committee of Kyushu University, and all subjects provided written informed consent before the start of the study.

Esophageal HRM protocol

Esophageal motility function was assessed by HRM using a Manoscan Z (Given Imaging, Los Angeles, CA, USA). HRM was performed using a previously described standardized protocol

[12]. After the basal condition without swallowing was recorded, subjects were instructed to swallow as infrequently as possible and to breathe quietly and regularly. Subsequently, subjects were asked to perform 10 swallows, each of 5 mL liquid, while in the supine position.

HRM data analysis

HRM data based on 10 swallows were analyzed using ManoView™ ESO 3.0 (Given Imaging). Subjects were diagnosed according to Chicago classification (CC) v2.0. LES function was measured by determining basal lower esophageal sphincter pressure (BLESP), integrated relaxation pressure (IRP), intrabolus pressure (IBP) at LES relaxation (LESR) and IBP average max. The contractile function of the esophageal body was determined by measuring the distal contractile integral (DCI), contractile front velocity (CFV) and distal latency (DL). Four patients with achalasia and two with absent peristalsis were excluded from the analysis of DCI. To determine the mechanism by which acotiamide improved esophageal motility function in patients with EGJOO, another original metrics, the swallow-induced LES relaxation rate was introduced since IRP was calculated with no reference to the LES pressure before swallowing. Swallow-induced LES relaxation rate (%) was defined by the following formula: (B-A)/B ×100, where A was minimal LES pressure for 10 sec after swallowing and B was mean LES pressure for 5 sec before swallowing. Namely, swallow-induced LES relaxation rate could indicate how much LES pressure was declined during deglutitive inhibition, assigning the gastric pressure and the mean LES pressure before each swallow to be 0 % and 100 %, respectively. We also assessed the extent of LES relaxation induced by pharyngeal water stimulation (PWS). LES pressure is known to be suppressed not only by

swallowing and belching, but also by PWS [13,14]. The extent of PWS-induced LES relaxation (mmHg) was assessed using the following formula: BLESP – A, where A was the mean LES pressure during PWS for 5 s, just before each liquid swallow.

Statistical analysis

All statistical analyses were performed using JMP 11.2.1 statistical software (SAS Institute, Cary, NC, USA). Data are expressed as median (range). The Wilcoxon signed-rank test was used to compare the values between before and after the treatment of acotiamide. Data in more than two groups were compared by analysis of variance (ANOVA), followed by Dunnett's test. P <0.05 was considered statistically significant.

Results

Clinical characteristic of the patients and HRM diagnosis based on CC ver2.0

The clinical characteristics of the patients are shown in Table 1. The 29 patients included 16 females and 13 males, of mean age 63.2 ± 2.8 years, mean height of 157.7 ± 1.3 cm and mean body weight of 50.0 ± 1.8 kg. Their mean body mass index (BMI) was 20.0 ± 0.6 kg/m^2, and their mean FSSG score was 19.9 ± 2.3, which was much higher than 7, the upper limit of normal [11]. EMDs were diagnosed of EMDs based on CC ver2.0 (Table 1). Four patients were diagnosed as normal. Of the remaining patients, four were diagnosed with achalasia, including three following pneumatic dilatation; six were diagnosed with esophagogastric junction outflow obstruction (EGJOO), four with distal esophageal spasm, two with absent peristalsis and seven with frequent failure of peristalsis.

Effects of acotiamide on esophageal motility function

To evaluate the effects of acotiamide on esophageal motility function, several HRM parameters were compared before and after administration of acotiamide (Table 2). Assessment of all 29 patients found that acotiamide had no effect on BLESP, which was 28.4 ± 1.9 mmHg before and 27.1 ± 1.8 mmHg after treatment with acotiamide. Mean levels of IRP, IBP at LESR and IBP average max before treatment were 13.6 ± 1.2 mmHg, 7.1 ± 0.55 mmHg and 17.8 ± 1.5 mmHg, respectively, whereas their mean levels after treatment were 11.5 ± 0.73 mmHg, 4.9 ± 0.64 mmHg and 13.0 ± 1.4 mmHg, respectively. Acotiamide tended to reduce IRP, IBP at LESR and IBP average max, but the differences were not statistically significant. In contrast, CFV and DL, which were markers of esophageal body contractility, did not differ significantly from before to after treatment with acotiamide. The levels of DCI in the 23 included patients tended to be lower after (1901.7 ± 392.2 mmHg-cm-s, n=23) than before that (1661 ± 377.2 mmHg-cm-s) acotiamide treatment, but the difference was not statistically significant. FSSG score was significantly lower after (14.2 ± 2.4) than before (19.8 ± 2.5, n=29) treatment. Thus, taken together, an analysis of all 29 patients showed that acotiamide had no effects on esophageal motility function.

Effects of acotiamide on esophageal motility functions in individual esophageal motility disorders

As the 29 patients included those with various types of EMDs, the effects of acotiamide on patients with each EMD type were determined. Patients with weak and absent peristalsis were excluded from this analysis because only two patients each had these disorders. BLESP was similar before and after treatment with acotiamide not only in normal subjects but also in

those with EMDs, including achalasia, EGJOO, DES and frequent failed peristalsis (Figure 1A). In the six patients with EGJOO, acotiamide dramatically reduced the levels of IRP, from 21.1 ± 2.4 mmHg before to 11.5 ± 1.4 mmHg, and those of DCI, from 3329.7 ± 1054.2 mmHg-cm-s to 2251.7 ± 667.4 mmHg-cm-s) (Figure 1B and C). In contrast, acotiamide had not effects on IRP and DCI levels, both in normal subjects and in patients with other EMDs (Figure 1B and C). Interestingly enough, esophageal motility was normalized by acotiamide in five out of the six patients with EGJOO. Consistent with HRM findings, symptoms in patients with EGJOO were drastically improved by treatment with acotiamide, with the median FSSG score decreasing from 19.0 (6.0–38.0) before treatment to 9.5 (3.0–20.0) after treatment (Figure 1D). The FSSG questionnaire can be used to evaluate both reflux-related and dyspepsia-related symptoms, and both types of symptoms were similarly improved by acotiamide treatment. The median dyspepsia-related score decreased from 9.5 (2.0–17.0) to 4.5 (0–11.0), and the median reflux-related score decreased from 10.5 (4.0–21.0) to 5.0 (2.0–13.0).

Effects of acotiamide on swallow-induced LES relaxation rate in patients with EGJOO

One of the main characteristics of EGJOO is impaired swallow-induced LES relaxation with IRP above the normal limit. Acotiamide restored or at least improved the impaired swallow-induced LES relaxation in EGJOO. We analyzed the mechanism underlying this activity. As BLESP was not affected by acotiamide (Figure 1A), we hypothesized that acotiamide may augment the extent of swallow-induced LES relaxation. Indeed, we found that swallow-induced LES relaxation rate in the six patients with EGJOO was significantly

higher after (54.2 ± 4.8%) than before (37.7 ± 3.4 %) treatment (Figure 2), indicating that acotiamide significantly potentiated the extent of swallow-induced LES relaxation by 136 %.

Effects of acotiamide on PWS-induced LES relaxation in patients with EGJOO

IRP in the six patients with EGJOO was significantly lower after acotiamide treatment (12.1, range: 5.6–16.4 mmHg) compared with before (19.5, range: 15.1–30.8 mmHg). Given that acotiamide potentiated swallow-induced LES relaxation by 136%, other mechanisms may underlie the ability of acotiamide to normalize IRP levels in patients with EGJOO. However, the median BLESPs in the six patients with EGJOO were similar before (31.6, 26.8–50.4 mmHg) and after (30.6, 18.7–42.9 mmHg) treatment with acotiamide, suggesting that BLESP was unaffected by acotiamide (Figures 1A, 3A, 3B and 3C). We therefore examined if acotiamide had any effects on PWS-induced LES relaxation. Significant LES relaxation could be induced by PWS in four patients with normal findings on HRM (Figure 3C). Interestingly, PWS-induced LES relaxation was impaired before treatment in patients with EGJOO (Figure 3A and 3C), but PWS-induced LES relaxation was apparently observed at swallow 1, and was significantly potentiated with repeated liquid swallowing in EGJOO patients treated with acotiamide (Figure 3B and 3C).

The extent of PWS-induced LES relaxation before swallows 1 and 10 in the six EGJOO patients after acotiamide treatment (5.4, −3–11.7 mmHg and 11.6, 2.4–19.1 mmHg, respectively) were significantly higher than those prior to acotiamide (1.2, −5.9–6.3 mmHg and 1.2, −3.5–7.2 mmHg, respectively) (Figure 3C). The difference in PWS-induced LES relaxation at each swallow before and after acotiamide treatment was significant, but PWS-induced LES relaxation in EJGOO patients treated with acotiamide was still smaller

than in the four patients with normal findings on HRM (Figure 3C). Improvements in swallow-induced LES relaxation by acotiamide led to a decrease in DCI (Figures 1E and 3B) in EGJOO patients. Overall, these findings indicate that acotiamide restored impaired swallow-induced LES relaxation by improving not only the swallow-induced LES relaxation rate, but also PWS-induced LES relaxation in patients with EGJOO.

Discussion

Following the initial development of HRM for measuring esophageal motility [15,16], this technique has been improved and is now widely used in clinical practice [17,18]. This method, together with the development of the CC [1,2], has improved the diagnostic yield of EMDs. The etiology and pathogenesis of EMDs, however, remain obscure, and appropriate treatments that target the underlying cause of individual EMDs have not been identified. No medications in current use are sufficient to cure EMDs, making invasive methods necessary for the treatment of achalasia. These invasive methods include endoscopic pneumatic dilation, POEM, laparoscopic Heller myotomy and botulinum toxin injection [3-5]. To our knowledge, the present study is the first to show that acotiamide has therapeutic effects in patients with EGJOO.

Acotiamide is a newly developed prokinetic agent currently being used in clinical practice for the treatment of FD in Japan. The gastroprokinetic action of acotiamide has been attributed to its ability to increase acetylcholine concentrations at neuromuscular junctions. Acotiamide was found not only to inhibit AChE activity but to enhance acetylcholine release by acting as an antagonist for the M_1 and M_2 muscarinic receptors in the enteric nervous system [9,19]. Our results showed that acotiamide had therapeutic effects in patients with

EGJOO, but did not affect normal esophageal motility, consistent with a clinical trial in healthy subjects [10]. Acotiamide did not have therapeutic effects, however, in patients with achalasia, distal esophageal spasm and frequently failed peristalsis. Taken together, these results indicate that acotiamide is effective in treating some, but not all, EMDs, especially EGJOO, as well as having no effects in normal subjects. The desirable therapeutic effects of acotiamide were also associated with gastric motility functions. Although acotiamide did not significantly alter gastric emptying rate or nutrient tolerance in healthy subjects, it enhanced gastric emptying and gastric accommodation in patients with FD [9,19].

EGJOO is characterized by impaired swallow-induced LES relaxation in combination with preserved peristalsis [1,20]. The etiology and pathogenesis of EGJOO have yet to be fully determined. The impaired LES relaxation in EGJOO suggests that this condition is likely a variant of achalasia or its early stage [20,21]. Disorders of EGJ outflow obstruction have been defined by IRP higher than the normal limit [2]. These disorders have been classified into two entities, achalasia and EGJOO, characterized by the absence and presence, respectively, of preserved peristalsis [1]. Therefore, EGJOO is usually accompanied by elevated intrabolus pressure (IBP), which is considered a logical consequence of impaired relaxation, thus validating the determination of impaired EGJ relaxation [20]. As for treatment of EGJOO, the effects of non-invasive medications, such as L type Ca^{2+} channel blockers and NO derivatives, are limited in patients with EGJOO. Those patients with severe symptoms may undergo invasive treatments usually performed on patients with achalasia, including endoscopic dilation, intrasphincteric botulinum toxin injection, or myotomy [20,22], inasmuch as EGJOO may be a variant of achalasia. Although both achalasia and EGJOO are characterized by impaired LES relaxation, the effects of acotiamide differed in patients with

these two disorders. In contrast to its effects in patients with EGJOO, acotiamide did not affect impaired esophageal motility function in patients with achalasia. Although the etiologies of these disorders have not been determined, the distinct phenotypes of disorders of EGJ outflow obstruction may be associated with certain immmunotoxicity patterns [21]. Specifically, the cytotoxic immune response leading to aganglionosis is responsible for Type I/Type II achalasia, whereas the non-toxic immune response causing cytokine-mediated functional aberration, which is not associated with progression to agangliosis, is responsible for Type III achalasia. Importantly, EGJOO may be a precursor condition of both Types I/II and Type III achalasia [21]. If EGJOO and achalasia are regarded as early- and late- or end-stage disorders of EGJ outflow obstruction, respectively, it is reasonable that acotiamide may be effective only during the early stage of these disorders.

It was important to determine the mechanism by which acotiamide restored the impaired swallow-induced LES relaxation in patients with EGJOO. The opposing activities of excitatory and inhibitory vagal pathways play a role in coordinating esophageal smooth muscle contractility. Owing to its tonic contractile activity, the LES spontaneously develops a basal tone and relaxes or further contracts in response to various reflexes. As a result, LES pressure is determined by the net balance among myogenic tone and cholinergic excitatory and nitrergic inhibitory pathways. The present study identified at least two possible mechanisms by which acotiamide repaired impaired swallow-induced LES relaxation in EGJOO. First, acotiamide potentiated the swallow-induced LES relaxation rate in patients with EGJOO. Acotiamide may augment nitrergic inhibitory pathways and increase NO production, or may increase the NO sensitivity of the contractile apparatus in LES. Second, PWS-induced LES relaxation was impaired in patients with EGJOO, and this impairment was

successfully repaired by acotiamide. PWS-induced LES relaxation could be referred to as LES accommodation. Enhanced LES accommodation by acotiamide resembled improvements in impaired proximal stomach accommodation in FD patients [9], given that LES exhibits characteristics of tonic contraction, similar to the proximal stomach. Altered LES accommodation may underlie the pathogenesis of EGJOO. Acotiamide exerts prokinetic activity essentially by acting as an AChE inhibitor or as an antagonist of M_1 and M_2 muscarinic receptors. The reasons why acotiamide augments the swallow-induced LES relaxation rate and restores PWS-induced LES relaxation remain unclear. Inhibitory vagal pathway nerves originate from neurons in the caudal region of the dorsal motor nucleus of the vagus. The preganglionic neurons are cholinergic in nature and synapse on postganglionic nitrergic inhibitory neurons in the myenteric plexus. Acotiamide may thus potentiate the inhibitory vagal pathway by affecting preganglionic cholinergic neurons in the myenteric plexus. Alternatively, it may directly affect the LES and regulate its myogenic tone by as yet undetermined mechanisms. Further research is required to determine the detailed mechanisms whereby acotiamide normalizes impaired LES relaxation in EGJOO.

This study had several limitations. First, it was a single-blind pilot study performed at a single center, and further randomized placebo-controlled studies are needed to confirm the effects of acotiamide in patients with EGJOO. Second, we were unable to perform sub-analyses in patients with weak or absent peristalsis because of the small sample size. Further investigations are also required to determine the effects of acotiamide on esophageal motility function in specific EMDs.

In conclusion, acotiamide potentially normalized the impaired LES relaxation in patients with EGJOO, with no effect on normal esophageal motility patterns. Acotiamide not

only potentiated the swallow-induced LES relaxation rate, but also restored PWS-induced LES relaxation. Acotiamide thus has the potential to become a promising treatment for patients with EMDs, especially EGJOO.

Specific author contributions: K.M., E.I. and O.T. designed this study. K.M. and E.I. wrote the manuscript. K.M. and K.F. performed HRM. T.O. and K.N. critically revised the manuscript for important intellectual content.

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Disclosure statement:

The authors declare that they have no conflicts of interest.

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Figure legends

Figure 1

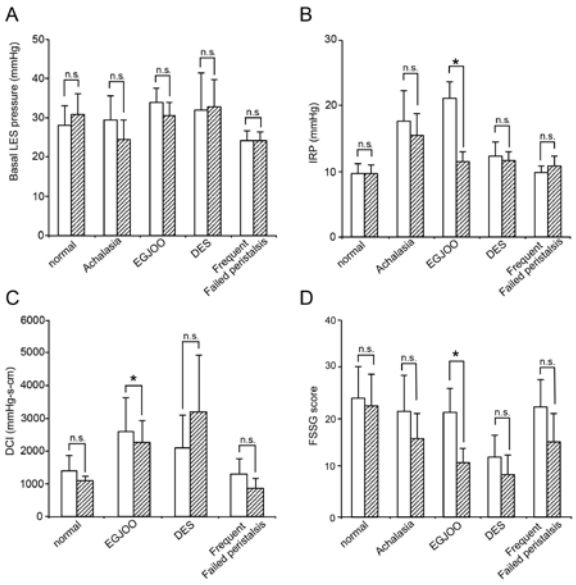

Figure 1 Effects of acotiamide on individual esophageal motility disorder.

A–D, Levels of basal lower esophageal sphincter (LES) pressure (A), integrated relaxation pressure (IRP) (B), distal contractile integral (DCI), (C) and FSSG score (D) before and after acotiamide treatment in patients with achalasia, EJG outflow obstruction (EGJOO), distal esophageal spasm (DES), frequent failed peristalsis, and in patients with normal HRM findings. DCI was not applicable in patients with achalasia. Data are shown as median (range). **P*< 0.05 vs. before acotiamide.

Figure 2

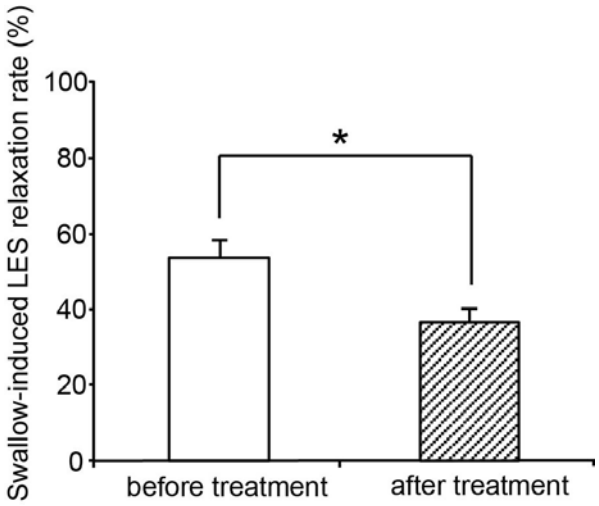

Figure 2 Effects of acotiamide on swallow-induced LES relaxation rate in patients with EJG outflow obstruction.

Swallow-induced LES relaxation rate was evaluated by determining the reduction in LES force level during deglutitive inhibition. The rate was calculated using the formula: (B−A)/B ×100, where A was minimal LES for 10 s after swallowing and B was the mean LES for 5 s before swallowing. Data are shown as median (range). *P< 0.05 vs. before acotiamide.

Figure 3

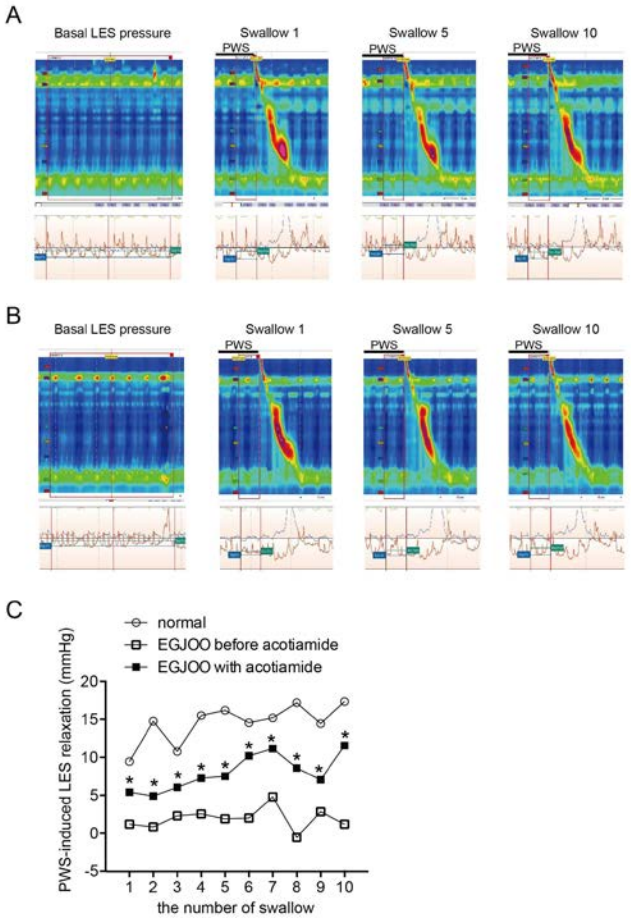

Figure 3 Effects of acotiamide on lower esophageal sphincter (LES) relaxation induced by pharyngeal water stimulation (PWS) in patients with EJG outflow obstruction (EGJOO).

A, B, Representative high-resolution manometry (HRM) spatiotemporal plots of EGJOO showing basal recording and swallows 1, 5, and 10 before (A) and after (B) treatment with acotiamide. Solid bar just prior to liquid swallow indicates PWS. Bold brown line plot indicates "virtual sleeve" measurement from LES. C, Summary of PWS-induced LES relaxation at each swallow in patients with normal HRM results (n=4) and those with EGJOO (n=6) before and after treatment with acotiamide. Median extent of PWS-induced LES relaxation was calculated for 5 s before each swallow. Data are shown as medians. **P*< 0.05 vs. before treatment.

Table 1. Clinical characteristics of the patients and HRM diagnosis based on Chicago classification (ver 2.0)

Clinical characteristics (n=29)	
Age (years)	63.2 ± 2.8
Sex (Female/Male)	16/13
Height (cm)	157.7 ± 1.3
Body weight (kg)	50.0 ± 1.8
Body mass index (kg/m^2)	20.0 ± 0.6
FSSG score (<7)	19.9 ± 2.3
HRM diagnosis [n (%)]	
Normal	4 (13.8)
Achalasia	4 (13.8)
EGJ outflow obstruction	6 (20.7)
Diffuse esophageal spasm	4 (13.8)
Weak peristalsis	2 (6.9)
Frequent failed peristalsis	7 (24.1)
Absent peristalsis	2 (6.9)

Results are reported as mean ± SEM or number (%)

Table 2. HRM findings before and after acotiamide treatment in all patients enrolled in the study (n=29)

HRM parameters	Before treatment	After treatment	
LES function			
Basal LES pressure (mmHg)	28.4 ± 1.9	27.2 ± 1.8	n.s.
4s-IRP (mmHg)	13.6 ± 1.2	11.5 ± 0.73	n.s.
IBP at LESR (mmHg)	7.1 ± 0.55	4.9 ± 0.64	n.s.
IBP average max (mmHg)	17.8 ± 1.5	13.0 ± 1.4	n.s.
Esophageal body contractility			
DCI (mmHg-cm-s)	1901.7 ± 392.2	1661 ± 377.2	n.s.
CFV (cm/s)	4.2 ± 0.59	3.2 ± 0.50	n.s.
DL (s)	7.0 ± 0.34	6.0 ± 0.63	n.s.

Results are shown as mean ± SEM.

Abbreviations: LES, lower esophageal sphincter; IRP, integrated relaxation pressure; IBP, intrabolus pressure; LESR, lower esophageal sphincter relaxation; DCI, distal contractile integral; CFV, contractile front velocity; DL, distal latency.

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