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Impact of Acotiamide Affects Meal-related Symptoms and Lower Abdominal Symptoms in Functional Dyspepsia in Japan

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Abstract

Background: To clarify whether acotiamide improve postprandial distress symptoms and lower abdominal symptoms through affecting hypothalamic-pituitary-adrenal (HPA) axis in FD patients.
Methods: We used Rome III criteria to evaluate upper and lower abdominal symptoms. Twenty-five functional dyspepsia (FD) patients were treated with acotiamide (300mg/day) for 4 weeks. Anxiety was evaluated using STAI-state/-trait. We measured ACTH and cortisol levels in FD patients.
Results: Acotiamide treatment significantly (p=0.007, p=0.003) improved postprandial fullness and early satiety in 4 weeks treatment in FD patients compared to those in pretreatment. In contrast, acotiamide treatment improved lower abdominal symptoms, while insignificantly. Acotiamide did not also affect anxiety using STAI-state/-trait. Acotiamide treatment for 4 weeks did not affect ACTH and cortisol levels in FD patients.
Conclusion: Further studies will be needed to clarify how acotiamide improve clinical symptoms in FD patients.

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Introduction

According to the Rome III criteria, the major symptoms of FD consist of bothersome postprandial fullness, early satiety, epigastralgia, and epigastric burning [1]. The symptom pattern and the underlying pathology of FD are heterogenous. Thus, visceral hypersensitivity in response to distention [2], impaired meal accommodation [3] and delayed gastric emptying has frequently been demonstrated in patients with FD [4-6]. Furthermore, the involvement of several other mechanisms has also been suggested, including duodenal hypersensitivity to the luminal contents, small bowel dysmotility, Helicobacter pylori infection [7], psychological disturbances [8] and central nervous system disorders [9]. Functional dyspepsia is treated by two major categories of drugs; acid inhibitors such as H2-receptor antagonists and proton pump inhibitors (PPIs), and prokinetic drugs which accelerate disturbed GI motility with modifying altered visceral sensitivity. However, the level of evidence for the efficacy of these approaches is low, and in particular there is a lack of prokinetic drugs of proven value for this condition.

Acotiamide hydrochloride (Z-338), N-[2-(bis(1-methyl-ethyl) amino)ethyl]-2-[(2-hydroxy-4,5-dimethoxybenzoyl)amino]thiazole-4-carboxamide monohydrochloride trihydrate, is a first-in-class drug which exerts gastroprokinetic activity by enhancement of acethylcholine release [1,10] via its antagonistic actions on the M1 and M2 muscarinic receptors [11], and partly by inhibiting acetylcholineesterase activity. Matsueda et al. reported that symptom improvement with the optimal dose of acotiamide 100mg t.i.d.was highest for meal-related symptoms, such as postprandial fullness, upper abdominal bloating and early satiation [12,13]. In animal models and in man, acotiamide enhances gastric emptying and gastric accommodation, two factors which have been implicated in the pathogenesis of PDS patients [1,10,11,14]. However, whether acotiamide alters gastric emptying and accommodation in FD patients is still an unsolved issue. Acotiamide may act directly on the gut and also indirectly through the brain-gut axis via actions in the central nervous system [14]. In this study, we aim to clarify whether acotiamide improve lower gastrointestinal tract symptoms as well as postprandial distress syndrome in FD patients through affecting hypothalamic-pituitary-adrenal (HPA) axis.

Material and Methods

Patients

Twenty-five patients presenting with typical symptoms of FD were enrolled after upper gastrointestinal endoscopy and abdominal ultrasonography. Patients were diagnosed according to Rome III criteria [15]. Twenty-five FD patients were treated with acotiamide (300mg/day) for 4 weeks. Exclusion criteria included severe heart disease, renal or pulmonary failure, liver cirrhosis, severe systemic illness and history of malignant disease. Patients with previous gastroduodenal surgery, duodenal ulcer scar, diabetes mellitus, and recent use of NSAIDs, PPIs or anticoagulants at endoscopy were also excluded. H. pylori infection was determined by both the 13C-urea breath test and by histological identification. Written informed consent was obtained from all subjects prior to undergoing upper gastrointestinal endoscopy and abdominal ultra-sonography for evaluation of their dyspeptic symptoms. The study protocol was approved by the Ethics Review Committee of Nippon Medical School Hospital.

Clinical symptoms

Clinical symptoms of FD were evaluated according to Rome III criteria [15]. Clinical symptoms must have involved at least one of the following: early satiation, bothersome postprandial fullness, epigastric pain, or epigastric burning. Diagnostic criteria for PDS included bothersome postprandial fullness occurring after ordinary-sized meals and/or early satiation that prevented completion of a

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normal meal, with either symptom occurring at least several times a week. Determination of diagnosis for EPS included all of the following: pain or burning that is intermittent localized to the epigastrium, and of at least moderate severity at least once per week. Diagnosis for PDS and EPS was fulfilled with symptoms occurring for the last three months and the onset of symptoms occurring at least six months prior to diagnosis. In this study, we enrolled PDS patients without abdominal pain or epigastric burning. FD symptoms and the feeling of hunger were assessed by visual analogue scale (VAS scale) [1,16-19]. FD patients was asked to grade the severity (visual analogue scale (VAS): 0-10; 0=absent, and 10=maximal) of FD symptoms (epigastric pain, epigastric burning, postprandial fullness and early satiety) based on modified previous study [18]. In addition, we assessed abdominal symptoms including constipation and diarrhea using the modified Gastrointestinal symptom Rating Scale (GSRS) [20].

State-Trait anxiety Inventory (STATI)

The STAI is a well-validated 40-item self-reported questionnaire to evaluate degree of anxiety [21]. The STAI is used to measure both state of anxiety (20 items) and trait of anxiety (20 items), wherein subjects choose one of four levels of anxiety for each item. State of anxiety reflects a "transitory emotional state or condition of the human organism that is characterized by subjective, consciously perceived feelings of tension and apprehension, and heightened autonomic nervous system activity." State of anxiety may fluctuate over time and can vary in intensity. In contrast, trait of anxiety denotes "relatively stable individual differences in anxiety proneness".

Measurement of plasma ACTH and cortisol levels in FD patients

A cannula was inserted into an anterior forearm vein and the patients were allowed to relax for 30 min. The cannula was kept patent by flushing with heparinized saline. Blood samples were obtained after an overnight fast of >12hr and the samples were immediately centrifuged and stored at -20°C until analysis. ACTH was measured using a commercially available two-site immunoradiometric assay. This is a non-extraction assay supplied by the Nichollas Institute, San Juan Capistrano, Calif., USA. The sensitivity of the assay is 5 ng/ml. Intra- and inter-assay coefficients of variation were 3 and 6%, respectively. The reliable lower limit of detection was 4.4 pmol/l (10ng/l). Cortisol was measured by an automated system using an enzyme immunoassay method (Immuno-I, Bayer Diagnostics, Newbury, UK). The sensitivity of the method is 10 nmol/l and has a between-batch variation of <5% over the range 50-1600nmol/l.

Statistical analysis

For statistical evaluation of group data, Students't-test for paired data and analysis of variance (ANOVA) for multiple comparisons were followed by Scheffe's F test. Mann-Whitney U test was used for analysis of categorical data. The distribution of alleles at each locus was assessed using the χ^2 Statistic of the Hardy-Weinberg equilibrium. To determine factors that associated with the disturbance of gastric emptying, multiple logistic regression analysis was used at 95% confidence intervals and associated p values. Data analyses were performed by using standard software package (SPSS version 13.0, Chicago, IL). A P value of less than 0.05 was statistically significant.

Results

Clinical symptoms in acotiamide-treated FD patients

Acotiamide treatment significantly (p=0.007 and p=0.003) improved postprandial fullness and early satiety (3.68±0.60, 3.68±0.544) as PDS symptoms in 4 week treatment compared to those in pretreatment (5.82±0.57, 5.18±0.58) (Figure 1). In contrast, acotiamide treatment did not (2.61±0.27, 1.92±0.98) significantly improved constipation and diarrhea score in 4 week treatment in FD patients compared to those in pretreatment (2.85±0.27, 2.18±0.248) (Figure 2).

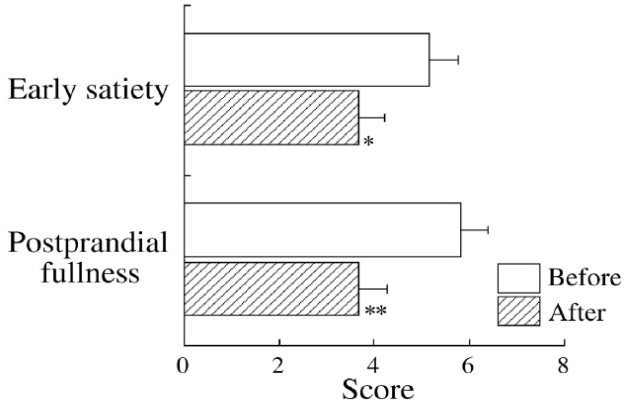

Figure 1: FD symptoms in acotiamide-treated FD patients.
Acotiamide treatment significantly (p=0.007 and p=0.003) improved postprandial fullness and early satiety in 4 week treatment compared to those in pretreatment.

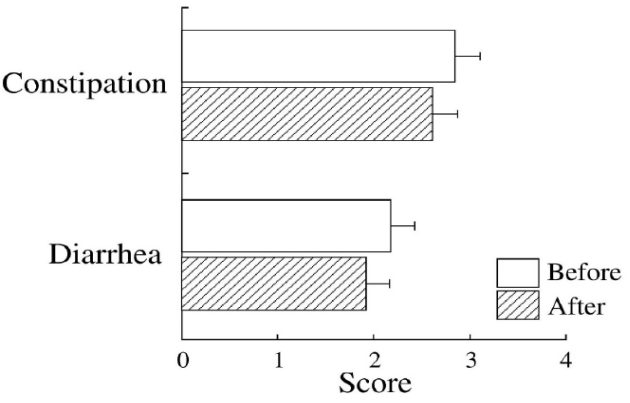

Figure 2: Comparison of lower GI tract symptoms in acotiamide-treated FD patients.
Acotiamide treatment did not (2.61±0.27, 1.92±0.98) significantly improved constipation and diarrhea score in 4 week treatment in FD patients compared to those in pretreatment (2.85±0.27, 2.18±0.248).

STAI-state/trait in acotiamide-treated FD patients

Since acotiamide treatment has been reported to improve FD symptoms, we tried to clarify whether acotiamide affect anxiety in FD patients. In this study, acotiamide treatment did not improved (47.48±6.20, 46.88±6.48) STAI-state/-trait in 4 week treatment in FD patients compared to those in pretreatment (47.27±6.01, 48.46±5.96) (Figure 3).

Comparison of the ACTH and cortisol in acotiamide-treated FD patients

To investigate, whether acotiamide improve FD symptom through

affecting hypothalamic-pituitary-adrenal (HPA) axis, we measured ACTH and cortisol levels in FD patients. Acotiamide treatment for 4 weeks did not significantly affect ACTH and cortisol levels (24.64±2.13 pg/ml, 12.37±0.72 μg/dl) in FD patients compared to those in pretreatment (24.80±2.64 pg/ml, 11.88±0.87 μg/dl) (Figure 4).

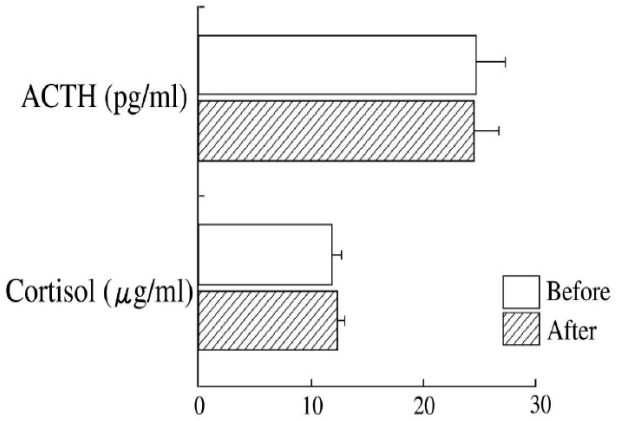

Figure 3: Comparison of STAI-state/trait in acotiamide-treated FD patients.
Acotiamide treatment did not improved STAI-state/-trait in 4 week treatment in FD patients compared to those in pretreatment.

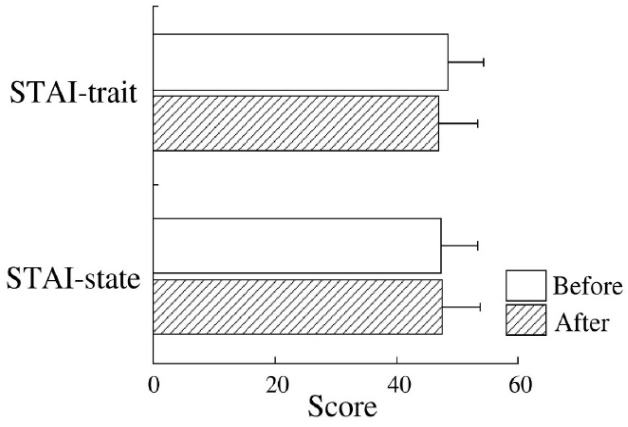

Figure 4: Comparison of the ACTH and cortisol in acotiamide-treated FD patients.
Acotiamide treatment for 4 weeks did not significantly affect ACTH and cortisol levels in FD patients compared to those in pretreatment.

Discussion

The major findings of this study are: 1) acotiamide treatment significantly improved postprandial fullness and early satiety in 4 weeks treatment, 2) acotiamide treatment for 4 weeks improved constipation score in FD patients, while insignificantly, 3) acotiamide treatment for 4 weeks did not affect ACTH and cortisol levels in FD patients.

In spite of higher prevalence of FD, treatment options for FD are very limited. Systematic reviews of the available literature have indicated that antisecretory drugs and prokinetic agents may be more effective than placebo in relieving FD symptoms [22,23]. Recent study has reported that acotiamide significantly improved PDS symptoms compared to placebo group [12,13,24,25]. There is no available data whether acotiamide affect FD symptoms and lower gastrointestinal (GI) tract symptoms. Therefore, in this study, we have first investigated whether acotiamide treatment is more effective for constipation score in FD patients. However, in our data, acotiamide treatment did not significantly improved lower GI tract symptoms. Previous studies have reported that acotiamide enhances acetylcholine release from enteric neurons through muscarinic receptor antagonism and acetylcholineesterase inhibition, thereby enhancing gastric emptying and gastric accommodation [26,27]. Nagahama et al have reported that oral administration of acotiamide stimulated postprandial gastroduodenal and colonic motor activities in conscious dogs [28]. Further studies will be warranted whether acotiamide improve lower GI tract symptoms using measuring lower GI tract motility as well as mosapride citrate reported in our previous study.

Conclusion

Altered gut-brain interactions may underlie symptom generation in FD patients. Activation of the hypothalamic-pituitary-adernal (HPA) axis followed by secretion of cortisol is considered as a physiological response to stress. HPA axis alterations and stress have been related to gut motor function [29]. However, the interaction between the free cortisol and other relevant variables in FD is scarcely known. Previous study has reported that changes in free cortisol secretion have corresponded to different symptoms of functional gastrointestinal disorders [30]. However, in our data, we could not find any significant differences in cortisol and ACTH levels in acotiamide alone group. Seto et al have also reported that in rat model, acotiamide did not alter adenocorticotropic levels [14]. These results suggest that FD patients did not have enough exposure to daily stress in order to activate the HPA axis and acotiamide treatment did not affect HPA axis in FD patients. Seto et al have reported that acotiamide exerted an impact on the expression of genes related to the expression of neuromedin U, known as a stress-related neuropeptide [14]. Acotiamide may act directly on organs of the gut and, indirectly on CNS via adjustment of the brain gut axis central and peripheral activity [11, 14, 31]. Further studies will be needed to clarify whether acotiamide affect gut hormones such as ghrelin and leptin.

Taken together, acotiamide treatment did not significantly improve lower GI tract symptoms and anxiety. Further studies will be needed to clarify whether long-term administration of acotiamide improve FD symptoms and gut motility.

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