ECRONICON OPEN ACCESS

EC GASTROENTEROLOGY AND DIGESTIVE SYSTEM

Review Article

Acotiamide: A Novel Prokinetic for Post-Prandial Distress Syndrome

Arif A Faruqui*

Department of Pharmacology, FI Maulana Ali Mian Institute of Medical Sciences, Bajehra, Lucknow, UP, India

***Corresponding Author:** Arif A Faruqui, Department of Pharmacology, FI Maulana Ali Mian Institute of Medical Sciences, Bajehra, Lucknow, UP, India.

Received: September 14, 2021; **Published:** October 29, 2021

Abstract

Functional dyspepsia is categorized as postprandial distress syndrome (PDS) - affiliated with meal intake, and epigastric pain syndrome (EPS), not affiliated to meal intake. However, at population level, PDS was reported to be the largest FD subgroup. Many treatments are available for management of PDS; however, the evidences level to establish its safety and efficacy is low. Moreover, the prokinetic drugs used for treatment of PDS are proven to be of least value for use. Acotiamide is a new prokinetic drug that was extensively studied in clinical trials and is approved by the regulatory authorities of Japan for the treatment of PDS. The gastroprokinetic effect of acotiamide is induced by enhanced ACh release through blocking of M1 and M2 muscarinic receptors in the enteric nervous system and inhibition of acetylcholinesterase activity. The following review summarizes the clinical efficacy and safety of acotiamide in relieving the symptoms of PDS.

Keywords: *Functional Gastrointestinal Disorders (FGIDs); Gastro-Intestinal (GI); Postprandial Distress Syndrome (PDS); Epigastric Pain Syndrome (EPS)*

Introduction

Functional gastrointestinal disorders (FGIDs) are chronic disorders of gastro-intestinal (GI) tract generally associated with GI symptoms without evidence of underlying structural, organic, or metabolic disease. These GI symptoms are general complaints of patients presented in outpatient department and are investigated during routine clinical investigations [1]. According to Rome III and IV, functional dyspepsia (FD) is heterogenous condition and further divided FD into - postprandial distress syndrome ((PDS) symptoms associated with meal intake such as, postprandial fullness and early satiation) and epigastric pain syndrome ((EPS) symptoms not associated with meal intake such as, epigastric pain and burning) [2,3]. However, this subdivision by Rome III was hampered due to overlap of both PDS and EPS symptoms [4]. Rome IV objectively diminished this overlap by considering all symptoms occurring post-prandially as PDS [3]. Thus, when patient complains of epigastric pain and other symptoms that occurs after meal (post-prandially), the patient is still diagnosed as suffering from PDS [5]. A 3-country survey including 5931 patients according to Rome IV consensus was conducted to determine the prevalence of FD. In this study, the incidence of FD ranged from 8 - 12%, of these 61% patients were detected with PDS, 18% with EPS and 12% with overlap of both syndromes [6]. Thus, at population level, PDS was observed as the largest FD sub-group.

Post-prandial distress syndrome

To understand the FD pathogenesis, a cluster of pathophysiological mechanisms have been proposed. These mechanisms include altered gastric sensorimotor function, mucosal changes and changes in processing of afferent signals from stomach by the brain (Figure 1). The various mentioned mechanisms reflect the heterogeneity of FD [4].

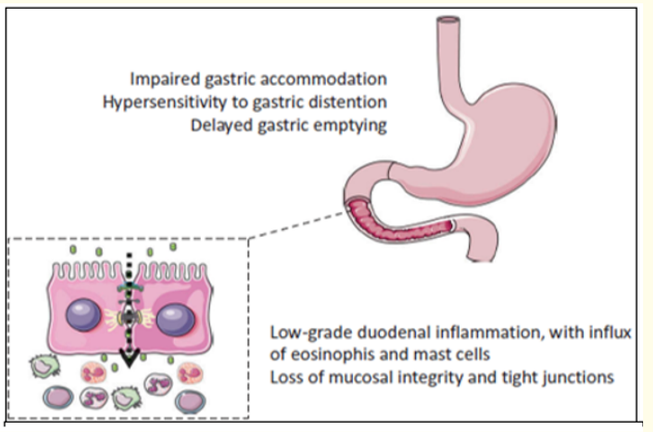

Figure 1: *Pathophysiological alterations in PDS [4].*

Diagnosis and treatment of PDS

Diagnosis

Based on the definition, FD can be detected only when upper GI examination is performed and the reports are negative [4]. At primary care clinics, patients are managed without endoscopy; thus, are considered as having 'uninvestigated dyspepsia' (Figure 2). Endoscopy is generally performed at the specialist level only on the presence of chronic symptoms. Diagnosis of FD is established on the basis of negative endoscopic results [2,3].

Treatment/management options

Diet control, such as more frequent small-sized meal and avoiding a fatty diet is generally recommended as PDS is associated with meal-related symptoms. However, clinical studies estimating the benefit of dietary interventions and other lifestyle changes are lacking [7].

PPI therapy for acid suppression remains the first-line therapy in FD management. Old clinical studies suggest that this treatment is more beneficial for EPS and overlapping GERD; whereas recent studies demonstrate conflicting results. Other treatments include a group of prokinetics; however, these treatments are less effective than PPIs for FD [8].

Very few prokinetic treatments are widely available. The design and quality of studies evaluating the efficacy and safety of these agents is extremely heterogeneous [8]. Older studies majorly includes: dopamine-2 antagonists (domperidone), serotonin-4 receptor agonists (cisapride (withdrawn due to QT interval prolongating effects)), and motilin receptor agonists (erythromycin, ABT-229) [4]. Other prokinetics such as itopride, mosapride, or tegaserod failed to demonstrate relevant benefit compared to placebo [8,9].

In patients with gastroduodenal symptoms and delayed emptying the correlation between symptomatic benefit and enhancement of gastric emptying rate is lacking [10] and available strong prokinetics may not be well-tolerated [9]. Thus, strong prokinetics should be considered in chronic cases where no satisfactory effects are reported with initial treatments and when patient is reported to have delayed gastric emptying (Figure 2) [4].

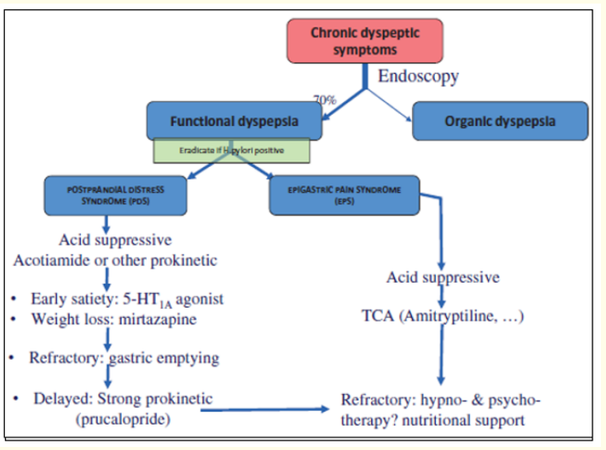

Figure 2: *Diagnosis and management of PDS [4].*

Necessity for new treatment options for PDS [11]:

- Various treatment strategies have been assessed for FD, including prokinetics for PDS.
- Acid suppressant agents showed better efficacy for EPS compared to PDS.
- However, evidence level is low for these approaches, and small number of prokinetic drugs are of proven value for this condition.
- Some prokinetics, such as cisapride and tegaserod, were withdrawn due to its cardiovascular side-effects.
- The dopamine antagonist metoclopramide has been associated with potentially important neurological side effects.
- Other prokinetics, such as itopride and mosapride failed to confirm superiority over placebo in controlled trials.
- Hence, there is a need for new therapeutic agent particularly for PDS.

Acotiamide: A novel gastroprokinetic

Acotiamide is a new prokinetic drug that was extensively studied in clinical trials, and which is approved by the regulatory authorities of Japan for the treatment of PDS [11].

Pharmacological actions

The gastroprokinetic effect of acotiamide is induced by enhanced ACh release through blocking of M1 and M2 muscarinic receptors in the enteric nervous system and inhibition of acetylcholinesterase activity. (Figure 3) [12].

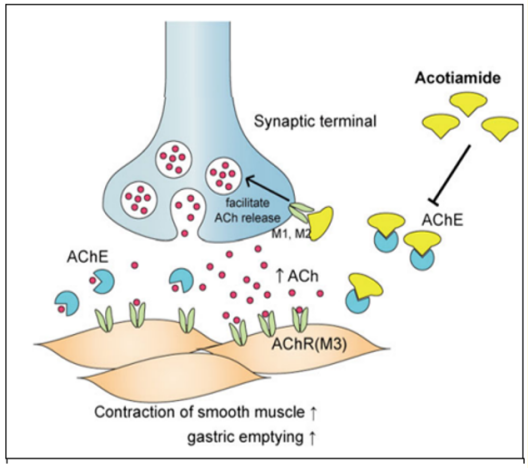

Figure 3: *Acotiamide: Mechanism of action [13].*

Various pharmacological effects of acotiamide on GI tract have been studied. *In vitro* study of acotiamide demonstrated that acotiamide at doses of > 10^{-6} M increases electrically stimulated contractions and release of Ach in the [3H]-choline-pre-incubated gastric antrum of guinea pig's stomach. Acotiamide inhibits human erythrocyte AChE activity reversibly; however the IC_{50} value was 100-fold lower than neostigmine and physostigmine. Acotiamide is reported to have affinity for dopamine receptor but not for the serotonin receptors, as observed in receptor binding studies. Thus, an important mechanism of acotiamide is facilitation of ACh release from cholinergic nerve terminals *via* inhibition of muscarinic M1 and M2 receptors [12].

Acotiamide was reported to alter the expressions of stress-related genes (GABA receptors, GABA transporters, and neuromedin U) in medulla oblongata or hypothalamus of rats induced with restrained stress. Thus, acotiamide may have potential role in stress regulation via modulation of hypothalamic-pituitary-adrenocortical axis activity [12].

Pharmacokinetics

Acotiamide reaches maximum plasma levels of 1 - 1.5h after ingestion. The plasma half-life of acotiamide is 7 - 10h. Acotiamide is excreted in the feces (45%). Steady state of acotiamide is reached after three cumulated doses for 100 and 300 mg, upon multiple dosing. Acotiamide has no significant inhibitory effect on cytochrome P450 [11].

Acotiamide: Safety and efficacy

Various studies had been conducted to document the efficacy and safety of acotiamide. Studies demonstrating efficacy and safety of acotiamide are enlisted in table 1.

Authors	Study Design	Patients and Dosage	Efficacy	Safety
Acotiamide: Clinical trials				
Jung DH., *et al*. [14]	A phase IIa, randomized, double-blind, placebo-controlled study	71 Patients Recruited from eight European centres Four arms Placebo or 50 mg, 100 mg and 300 mg t.i.d. of Acotiamide before the meal during 3 weeks Total duration 9 weeks: 2 weeks for run-in, wash-out and baseline, 3 weeks for treatment and 4 weeks for follow-up.	300 mg was better than placebo for meal accommodation. 100 mg was better than placebo at week 2 for upper abdominal bloating (P = 0.001). 100 mg was better than placebo for QOL (physical function) (P = 0.003).	Acotiamide was safe and well-tolerated in patients with FD. Acotiamide did not induce any QTc segment prolongation. No increase in prolactin levels. No extra pyramidal symptoms during or after the period of exposure to Acotiamide
Matsueda K., *et al*. [15]	Multicenter, open-label, single-arm, long-term (48 weeks) Phase III trial	409 Patients Conducted at 32 centers in Japan during a period of 17 months 100 mg t.i.d for 48 weeks	The Overall treatment efficacy (OTE) improvement rate was 26.1% at week 1 and increased with time. It was 60.6% at week 8 and subsequently maintained. Similarly, the symptom elimination rate increased up to week 8.	The incidence rate of adverse drug reactions was 11.5%. Most of the adverse drug reactions were mild.
Matsueda K., *et al*. [16]	Multi-centre,randomised, double-blind, placebo-controlled, parallel-group, Phase III trial	897 Patients 4-week treatment period and the 4-week post-treatment follow-up period Conducted at 67 centres in Japan over a period of 21 months 100 mg three times a day for 4 weeks	The responder rate based on the OTE was 52.2% for patients receiving Acotiamide and 34.8% with placebo (p<0.001). The elimination rate for all three meal related symptoms was 15.3% among patients receiving Acotiamide compared with 9.0% in the placebo group (p=0.004). Quality of life was significantly improved with 100 mg of Acotiamide as compared with placebo.	Acotiamide was well tolerated The incidences of adverse events were similar between the Acotiamide group and placebo group. Most adverse effects were mild or moderate in severity. The most commonly reported adverse events were increase of serum triglycerides, serum prolactin, or serum g-glutamyltransferase and nasopharyngitis.

Narayanan V., *et al*. [17]	Real-world study	1525 FD patients presented with multiple FD symptoms of post prandial fullness, early satiety along with other overlapping symptoms Acotiamide 100 mg thrice daily	Complete relief or significant improvement from upper abdominal (epigastric) pain, Upper abdominal (epigastric) discomfort, Upper abdominal bloating, excessive belching and heartburn was reported. Almost 50% of the patients obtained symptomatic relief with Acotiamide as early as 1-2 weeks of therapy Overall, symptomatic improvement with Acotiamide did not differ between groups with and without a PPI as co-therapy.	Adverse events were reported by 1.3% patients and were mild and transient in nature without need for cessation of Acotiamide.
Acotiamide: In new formulations				
Sinha S D., *et al*. [18]	Randomized, Double-Blind, Multicenter Study	219 patients with FD-PDS aged 18-65 years Patients were randomized to receive either acotiamide ER 300 mg once daily or acotiamide 100 mg three times daily for four weeks.	The responder rate for overall treatment effect (OTE) at the end of the 4 weeks: Acotiamide ER 300 mg OD: 92.66% Acotiamide 100 mg TID group: 94.39% (97.5% CI −8.3,4.8), in per-protocol (PP) In intent to treat population, Acotiamide ER 300 mg OD: 92.66% Acotiamide 100 mg TID group: 92.73% (97.5% CI −7.0,6.8), in intent to treat (ITT) population	Adverse events were reported by 7.9% of patients in acotiamide ER 300 mg and 9.2% in acotiamide 100 mg patients The most common adverse event reported was a headache
Acotiamide vs. Levosulpiride				
Behera R., *et al*. [19]	A prospective, cohort study conducted for 8 week	60 patients with symptoms of FD Patients were divided in two groups: Group A: 100mg acotiamide TDS before meal for 8wks. Group B: Levosulpiride 25 mg TDS for 8 wks.	Patients treated with Acotiamide showed more improvement in symptoms of FD in comparision to Levosulpiride.	Patients treated with Acotiamide showed better toleratance to Acotiamide compared to Levosulpiride

Table 1

Conclusion

- Acotiamide is a novel prokinetic agent marketed for its use in patients with FD.
- Acotiamide was evaluated in FD in Phase II and Phase III studies in Europe, Japan and the USA.
- The efficacy and safety of Acotiamide ER 300 mg once daily were observed to be comparable to Acotiamide immediate release 100 mg thrice daily.
- Acotiamide is promising gastroprokinetic agent for FD because of its efficacy without any significant side-effects.
- The safety and tolerability profile to date is excellent.
- Acotiamide has better efficacy and safety profile compared to levosulpiride.

Bibliography

1. Tack J and Drossman DA. "What's new in Rome IV?" *Neurogastroenterology and Motility* 29 (2017): e13053.
2. Tack J., *et al*. "Functional gastroduodenal disorders". *Gastroenterology* 130.5 (2006): 1466-1479.
3. Stanghellini V., *et al*. "Gastroduodenal disorders". *Gastroenterology* 150 (2016): 1380-1392.
4. Van Den Houte K., *et al*. "Postprandial distress syndrome: stratification and management". *Expert Review of Gastroenterology and Hepatology* 13.1 (2019): 37-46.
5. Carbone F., *et al*. "Rome III functional dyspepsia subdivision in PDS and EPS: recognizing postprandial symptoms reduces overlap". *Neurogastroenterology and Motility* 27.8 (2015): 1069-1074.
6. Aziz I., *et al*. "Epidemiology, clinical characteristics, and associations for symptom-based Rome IV functional dyspepsia in adults in the USA, Canada, and the UK: a cross-sectional population-based study". *Lancet Gastroenterology and Hepatology* 3.4 (2018): 252-262.
7. Feinle-Bisset C and Azpiroz F. "Dietary and lifestyle factors in functional dyspepsia". *Nature Reviews Gastroenterology and Hepatology* 10.3 (2013):150-157.
8. Moayyedi PM., *et al*. "ACG and CAG clinical guideline: management of dyspepsia". *The American Journal of Gastroenterology* 112.7 (2017): 988-1013.
9. Tack J. "Prokinetics and fundic relaxants in upper functional GI disorders". *Current Opinion in Pharmacology* 8.6 (2008): 690-696.
10. Janssen P., *et al*. "The relation between symptom improvement and gastric emptying in the treatment of diabetic and idiopathic gastroparesis". *The American Journal of Gastroenterology* 108.9 (2013): 1382-1391.
11. Altan E., *et al*. "Acotiamide, a novel gastroprokinetic for the treatment of patients with functional dyspepsia: postprandial distress syndrome". *Expert Review of Gastroenterology and Hepatology* 6.5 (2012): 533-544.
12. Ueda M., *et al*. "Profile of acotiamide in the treatment of functional dyspepsia". *Clinical and Experimental Gastroenterology* 9 (2016): 83-88.
13. Matsushita M., *et al*. "Emerging treatments in neurogastroenterology: Acotiamade, a novel treatment option for functional dyspepsia". *Neurogastroenterology and Motility* 28.5 (2016): 631-638.
14. Jung DH., *et al*. "Effects of GC7101, a Novel Prokinetic Agent on Gastric Motor Function: Ex Vivo Study". *Journal of Neurogastroenterology and Motility* 20.4 (2014): 469-474.
15. Matsueda K., *et al*. "A long-term study of acotiamide in patients with functional dyspepsia: results from an open-label phase III trial in Japan on efficacy, safety and pattern of administration". *Digestion* 84.4 (2011): 261-268.

16. Matsueda K., *et al*. "A placebo-controlled trial of acotiamide for meal-related symptoms of functional dyspepsia". *Gut* 61.6 (2012): 821-828.

17. Narayanan V., *et al*. "Real World Efficacy and Tolerability of Acotiamide, in Relieving Multiple and Overlapping Symptoms in Patients of Functional Dyspepsia". *Archives of Gastroenterology and Hepatology* 1.1 (20018): 1-6.

18. Sinha S D., *et al*. "Efficacy and Safety of Orally Administered Acotiamide Extended-Release Tablets Among Functional Dyspepsia-Postprandial Distress Syndrome Patients: A Randomized, Double-Blind, Multicenter Study". *Cureus* 13.4 (2021): e14361.

19. Behera R. "Efficacy and Safety Assessment of Acotiamide and Levosulpiride in Functional Dyspepsia". *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)* 16.11 (2017): 53-57.

Volume 8 Issue 11 November 2021