Archives of Gastroenterology and Hepatology

Volume 1, Issue 1, 2018, PP: 1-6

Real World Efficacy and Tolerability of Acotiamide in Relieving Multiple and Overlapping Symptoms in Patients of Functional Dyspepsia

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Abstract

***Background:** Functional Dyspepsia (FD) is a common clinical conditionthat can significantly affectquality of life. Patients present withmeal-related FD symptoms like post-prandial fullness, and early satiety (PDS type) and/or epigastric pain/discomfort (EPS type), however common presentation is with a mix of both EPS and PDS symptoms which can also coexist with abdominal bloating, heartburn and belching. This often poses a therapeutic challenge for the clinicians as poorly-defined and overlapping symptoms can hamper effective treatment selection. Acotiamide is a first-in-class drug that exerts its gastro-kinetic effect by enhancing acetylcholine release. Evidence from randomized clinical studies as well as real world in clinic data capture is available for its efficacy and tolerance in relieving meal related PDS type symptoms however data on effects of Acotiamide on other commonly coexisting symptoms like abdominal pain/discomfort, bloating, belching and heartburn as seen commonly inreal world,is currently lacking.*

***Methodology:** In this study, 1525 FD patients visiting 148 gastroenterology clinics across India, received Acotiamide 100 mg thrice daily. These patients were assessed by the treating physician for patient's perception of improvement in the presenting symptoms, as well as tolerance to treatment.*

***Results:** Complete relief or significant improvement from Upper abdominal (epigastric) pain, Upper abdominal (epigastric) discomfort, Upper abdominal bloating, Excessive belching and Heartburn was seen in 65.5%, 75.5%, 77.4%, 68.7% and 64% patients respectively. (P<0.001 for all mentioned values versus no/slight improvement). 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.*

***Conclusion:** This real-world study suggests that use of Acotiamidecan also improve overlapping symptoms of upper abdominal pain, bloating and discomfort, belching and heartburn which often coexist with meal related PDS type symptoms in FD patients.*

Keywords: *Rome Criteria, Functional Dyspepsia, Acotiamide, Overlapping, Upper Abdominal Pain, discomfort, Bloating, Belching, Heartburn*

Introduction

Functional Dyspepsia (FD) represents a condition of impaired digestion with the presence of bother some dyspeptic symptoms of Postprandial Distress Syndrome (PDS) mainly composed of early satiation or postprandial fullness, and Epigastric Pain Syndrome (EPS), mainly composed of epigastric pain/discomfort or burning, in the absence of an organic, structural

or metabolic disease to explain these symptoms. FD is known to be a heterogeneous disorder, with multiple pathogenic factors, such as excessive gastric acid secretion, gastric motility disorder, Helicobacter pylori infection, psychological factors and visceral hypersensitivity[1].

The prevalence of functional dyspepsia worldwide is about 20-30% (representing 60% of the dyspepsia patient pool).[2]About one third of FD patients present with delayed gastric emptying.[3]with or without delayed acid clearance. Around 9% and 27% of FD patients present exclusively with EPS and PDS type FD respectively but majority (64% patients) present with overlapping PDS and EPS symptoms.[4]GERD symptoms (mainly heartburn and belching) have also been seen to overlap with FD symptoms in up to 25% patients and this subset of patients often are refractory to PPIs.[5]In clinical practice, patients commonly describe in various ways an abdominal or epigastric discomfort not amounting to typical epigastric pain or burning. Some patients with FD symptoms and delayed gastric emptying may also have associated constipation.[6]

Acotiamide is a first-in-class gastroprokinetic agent extensively studied in clinical trials. It improves upper gastrointestinal motility to relieve abdominal symptoms arising due to impaired GI motility in FD patients. Acotiamide received its first global regulatory approval in Japan in 2013 and was approved in India in 2016 for the treatment of bloating after meals, epigastric bloating and early satiety in FD patients and is listed in Rome IV as a treatment option for FD[7]. Gastroprokinetic action of Acotiamide results from enhancedaction of acetylcholine (ACh) by antagonizingpre-synaptic enteric M1 and M2 muscarinic receptors,as well as by inhibiting acetylcholinesterase activity thereby prolonging the availability and action of the ACh. Acotiamide does not appear to be associated with prolongation of the QTc interval and does not show marked CYP inhibition. Approximately, 45% of Acotiamide is excreted in the feces with a plasma half-life of 7–10 hours.[8]

Randomized controlled clinical trials for Acotiamide have usually excluded patients with overlapping symptoms. The phase 2 studies in US as well as long term phase 3 studies in Japan and Europe have mainly studied patients with PDS-FD.[9,10,11]We had recently conducted and published the real world in clinic data capture of the efficacy and tolerance of Acotiamide in meal related symptoms (PDS type FD).[12] Given the high rate of overlapping meal related, epigastric and reflux symptoms in day to day practice, it would be particularly relevant to see how Acotiamide fares in the real world in relieving these symptoms apart from meal related symptoms ofearly satiation and postprandial fullness, for which the efficacy and tolerance of Acotiamide is already well documented. To our knowledge this is the first real world analysis of Acotiamide in this subset of FD patients with multiple overlapping symptoms.

Methodology

1525 adult patients who presented clinically with multiple FD symptoms of post prandial fullness, early satiety along with other overlapping symptoms including upper abdominal (epigastric) pain/ burning, Upper abdominal (epigastric) discomfort, Upper abdominal bloating, Excessive belching and Heartburn in the Gastroenterologist's out-patient department and were prescribed 100mg Acotiamide thrice daily, were assessed by the treating physician with a questionnaire to capture patient's perception of improvement in the presenting symptoms, as well as tolerance to treatment.

The data was capturedfrom 148 Gastroenterologists across India (71 in north, 34 in east zone, 24 in west zone and 19 in south zone). To facilitate objective and unambiguous assessment by the patients, a 4-point rating scale, comprising of (a) 'No improvement', (b) 'Slightly improved', (c) 'Significantly improved', and (d) 'Complete relief', was used. For each patient, the duration of treatment and co-prescribed therapies was also recorded. Adverse events, if any, were recorded, assessed and managed. All patient-data was captured in accordance with ethical principles and with patient consent.

Results

1525 patients were prescribed Acotiamide for their FD symptoms. 66.6% were male patients, and 57.7% patients were ≥40 years while 15% patients were ≥ 60 years. 39% and 57% patients presented with symptoms of early satiety and postprandial fullness. The percentage of patients presenting with other overlapping symptoms was as follows: Upper abdominal (epigastric) pain (1036) 68%, Upper

abdominal (epigastric) discomfort (1077) 70.6%, Upper abdominal bloating (1118) 73.3%, Excessive belching (870) 57%, and Heartburn (858) 56.2%.

Complete relief or significant improvement from Upper abdominal (epigastric) pain, Upper abdominal (epigastric) discomfort, Upper abdominal bloating, Excessive belching and Heartburn was seen in 65.5%, 75.5%, 77.4%, 68.7% and 64% patients respectively. (P<0.001 for all mentioned values versus no/slight improvement – Figure 1).

No significant difference in complete relief or significant improvement rates was seen between men and women, or for patients aged <40 and ≥40 years or <60 and ≥60 years for all the symptoms assessed.

The pre-therapy duration of symptoms (≤6 months or >6 months) did not significantly affect the scorings of complete relief or significant symptomatic improvement seen for upper abdominal discomfort and bloating. However, for upper abdominal pain, belching and heartburn, significantly more patients in the group with symptom duration less than 6 months, achieved complete or significant relief.

The symptomatic relief with Acotiamide was seen to be obtained as early as 1-2 weeks of therapy with 50%, 58.9%, 52.2%, 45.2% and 49.4% patients obtaining significant relief from Upper abdominal (epigastric) pain, Upper abdominal (epigastric) discomfort, Upper abdominal bloating, Excessive belching and Heartburn respectively after 7-14 days of Acotiamide therapy.

A sub-analysis was also performed comparing the symptomatic improvement rates in patients who were given a PPI as co-therapy along with Acotiamide and those that were not. Being real world data, co-prescriptions of PPI in patients with overlapping symptoms is expected and common. Significantly higher number of patients achieved complete relief from upper abdominal bloating, when given Acotiamide alone as compared to those patients prescribed both Acotiamide and PPI (P=0.007) while this difference was not significant for the other symptoms. The number of patients who showed no improvement/no relief from upper abdominal pain, heartburn and belching were significantly more in the Acotiamide group not prescribed PPI as compared to those patients given PPI as co-therapy (P=0.018, 0.0005 and 0.04 respectively), however no difference was seen for these symptoms for patients achieving complete or significant relief between the groups with and without co-therapy.

Adverse events were reported by 1.3% patients, which were mainly nausea, vomiting, abdominal cramps, diarrhoea and constipation, all of which were mild and transient in nature and most did not require cessation of Acotiamide. Treatment discontinuation occurred in 23 patients (16 due to cost, 5 due to perceived lack of adequate symptomatic relief, 1 each due to diarrhoea and development of another comorbid condition).

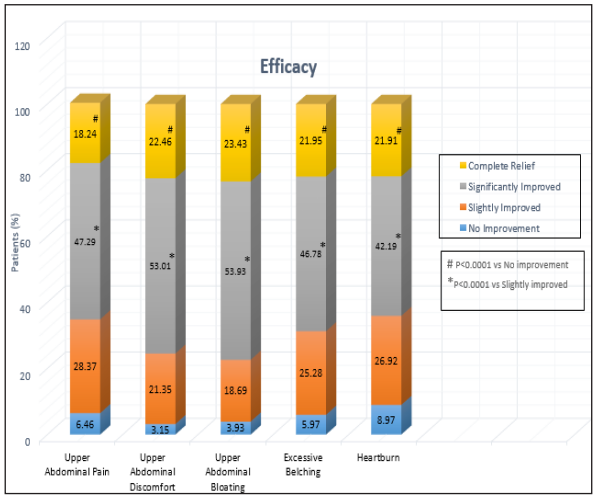

Figure 1. *Physician's assessment of patients' symptomatic improvement*

Discussion

Acotiamideacts by improving gastric emptying and accommodation, thereby, relieves meal related FD symptoms.Studieshavealsodemonstratedthemechanism of action of Acotiamide on gastric accommodation and gastric emptying by gastric ultrasound and scintigraphy which found significant difference in the improvement of gastric accommodation between the Acotiamideand placebo (21.7% vs 4.4% by placebo), and significantly accelerated gastric emptying (50 % half-emptying time- P = 0.02 vs. 0.59 for placebo).[13,14]

Randomized control studies with Acotiamide have been done in patients with mainly PDS type (meal related) FD symptoms: post prandial fullness and early satiety. The US phase 2b study of Acotiamide included patients who did not show response to PPI, post a trial run in two-week period.[6] The overall treatment evaluation (OTE) was significantly better for Acotiamide 300mg/day as compared to placebo,

as seen at 4 and 12 weeks.[9] In the long term European phase 3 study, OTE improvement for meal related FD symptoms increased from 13.1% at Week 1 to 41.5% at Week 12, then increased further to 70.2% at Week 52. 81.6% of patients, maintained exposure to Acotiamide for >50 weeks, with a mean duration of 320.3 days.[10]

Similarly the Japanese phase 3 study showed an OTE improvement rate of 26.1% at week 1 which increased with time reaching 60.6% at week 8, and improving consistently to 66.7% at week 48 and 73.2% (during the last period of treatment)[11] Placebo controlled study for Acotiamide showed an OTE improvement rate of 52.2 % patients receiving Acotiamide and 34.8 % patients receiving placebo ($p<0.001$) which was well maintained for 4 weeks post withdrawing treatment.[15]Acotiamide was well tolerated in all these studies.

Recently a real-world study in 314 patients presenting with meal related FD symptoms evaluated the improvement perception by patients on a 4-point scale across 63 gastroenterology clinics across India.[12]Complete relief or significant improvement from post prandial fullness, upper abdominal bloating and early satiety was achieved by 79.2%, 74.4%, and 77.1% patients respectively. ($P<0.001$ for all versus no/slight improvement). Significantly more number of patients achieved complete relief when treated for >28 days or 14-28 days than when treated for less than 2 weeks ($P<0.05$). Acotiamide was well tolerated in this study with only 2 patients discontinuing treatment.

Acotiamide100mg tidhas also been compared with Levosulpiride 25mg tid in 60 Indian FD patients[16] Approximately 93% patients reported excellent to good improvement of FD symptoms after a 4-week administration of Acotiamide compared to 80% improvement with Levosulpiride. The study concluded that, Acotiamide was superior to Levosulpiride in, both, efficacy and tolerability in FD patients[16].

Acotiamidehas also been evaluated in combination with PPIs.In one study, 78% of FD patients with residual symptoms post standard treatment with Esomeprazole, achieved an overall improvement in symptoms after 2 weeks of combination therapy of Esomeprazole and Acotiamide.[17] Almost all FD-related symptoms statistically improved after the combination therapy, with an improvement in the mFSSG score relevant to the postprandial distress syndrome and epigastric pain syndrome. In another study, patients showing overlapping symptoms between GERD and FD experiencing heartburn and epigastric fullness symptoms after standard-dose Rabeprazole for ≥ 8 weeks were evaluated with a combination ofAcotiamide 100mg tidplus Rabeprazole 10mg od versus double dose Rabeprazole 20mg alone.[5] The three upper gastrointestinal symptoms (heartburn, epigastric pain, and epigastric fullness) were reduced by ≥ 50% in 40.8% and 46.9% of patients in the combination (Acotiamide with standard dose PPI), and PPI double-dose groups, respectively, with no significant difference between the two groups. Therefore, these studies show that adding Acotiamide to a standard dose PPI can be an effective option to doubling PPI dose in patients of FD with heartburn, and that combination therapy of Acotiamide and PPI may be effective in selected FD patients with insufficient improvement with an initial PPI.

Our current real-world study has shown that Acotiamide can be an effective choice in a variety of FD patients who present in a physician's OPD with multiple upper GI symptoms. This is the first time to our knowledge that the clinical effectiveness of Acotiamide has also been studied in symptoms other than the typical PDS symptoms for which it has been studied in global randomized controlled studies.

The evidence of the efficacy and safety of Acotiamide use in relieving meal related symptoms of early satiety and post-prandial fullness has been consistently demonstrated in many clinical trials and accordingly regulatory approval globally has been received for the same.[18]Though Acotiamide does not have evidence in GERD management, our study showed improvement in epigastric pain, heartburn and belching symptoms with Acotiamide possibly due to enhanced acid clearance and gastric emptying, however adding a PPI to Acotiamidefor these symptoms can significantly reduce the number of non-responders. Acotiamide alone relieved abdominal bloating better than when a PPI was added. There is evidence to suggest that PPI can decrease gastric emptying especially that of solids, which could explain this particular result.[19,20]In all other symptoms assessed including epigastric pain and discomfort, Acotiamide fared as well alone as with

an added PPI. In relief of meal related symptoms, both RCT and real-world data have shown better responses with longer duration of treatment. In our study there was no significant difference in the number of patients who achieved complete or significant symptomatic relief at 7-14 days as compared to 14-28 days or more suggesting an early response of these overlapping symptoms to Acotiamide. This real-world study further confirms the safety and tolerance of Acotiamide seen with various published studies, and both the rate of adverse events and treatment discontinuations were minimal.

Findings of this study will assist clinicians commonly seeing dyspeptic patients in general and specialized practice, with multiple overlapping symptomatology affecting the patients' quality of life.

More real-world studies are thus welcome in even larger population size and diverse ethnicities with, longer follow up periods to continuously guide treating physicians on effective therapy choices for theirpatients.

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Citation: **Varsha Narayanan, Shailesh Pallewar, Maneesha Khalse, Amit Bhargava**. *Real World Efficacy and Tolerability of Acotiamide, in Relieving Multiple and Overlapping Symptoms in Patients of Functional Dyspepsia. Archives of Gastroenterology and Hepatology. 2018; 1(1): 1-6.*