ORIGINAL RESEARCH PAPER
VOLUME-6 | ISSUE-5 | MAY - 2017 | ISSN No 2277 - 8179 | IF : 4.176 | IC Value : 78.46
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

Acotiamide: A novel drug for the treatment of patients with functional dyspepsia.

Pharmacology

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ABSTRACT

Functional dyspepsia (FD) is a highly prevalent condition with major socioeconomic and healthcare impact. Previously, no pharmacotherapeutic agent has been approved for the treatment of this condition. Acotiamide, a new first-in-class oral prokinetic drug, is an upper gastrointestinal motility modulator for the treatment of abdominal symptoms resulting from hypomotility and delayed gastric emptying in patients with functional dyspepsia. It exerts its activity in the stomach via muscarinic receptor inhibition, resulting in enhanced acetylcholine release and inhibition of acetylcholinesterase activity. Unlike other prokinetic drugs that are utilized in the management of functional dyspepsia, acotiamide shows little/no affinity for serotonin or dopamine D2 receptors. Acotiamide is the world's first approved treatment for functional dyspepsia diagnosed by Rome III criteria, with its first approval occurring in Japan. A favorable clinical course with acotiamide 100 mg t.i.d was demonstrated with high symptom elimination rate for patients of FD

KEYWORDS:

Functional Dyspepsia, Acotiamide, Acetylcholine

Functional dyspepsia (FD) is a highly prevalent condition with major socioeconomic and healthcare impact. The Rome consensus proposed to subdivide FD into postprandial distress syndrome (PDS), characterized by meal-related symptoms and epigastric pain syndrome (EPS), characterized by pain and burning. The dyspeptic symptoms are epigastric pain, epigastric burning, postprandial fullness, early satiation and others, including bloating in the upper abdomen, nausea, vomiting and belching.[1]

The pathogenesis of functional dyspepsia is not fully elucidated and, with the limited pharmacological options available for its treatment, explains the controversy regarding the best approach to its management. Current management strategies recommend dietary and lifestyle modifications in those with mild, intermittent symptoms, testing for and eradication of *Helicobacter pylori* and, in those with severe symptoms, first-line pharmacotherapy with a prokinetic agent (e.g. cisapride, tegaserod, domperidone, acotiamide) and then a proton pump inhibitor (PPI; e.g. Pantoprazole) in those with PDS, with these two classes of drugs considered in the reverse order (i.e. a PPI, then a prokinetic drug) in those with EPS.

A review of the use of cisapride and domperidone for FD revealed their benefits than for placebo [2]. (Cisapride has since been withdrawn due to safety concerns.)

Acotiamide, a new first-in-class oral prokinetic drug, is an upper gastrointestinal motility modulator for the treatment of abdominal symptoms resulting from hypomotility and delayed gastric emptying in patients with functional dyspepsia. Its mode of action differs from that of other widely utilized prokinetic drugs (e.g. cisapride which primarily acts via serotonin 5HT4 receptors) in that it is unrelated to dopamine D2 or serotonin receptor activity, for which the drug exhibits very low affinity. The drug was approved in Japan in March 2013 and launched in Japan in June 2013, making it the world's first approved treatment for functional dyspepsia in patients diagnosed by Rome III criteria.

Pharmacodynamics

Acotiamide is a novel gastroprokinetic drug that exerts its activity via muscarinic receptor inhibition, which results in enhanced acetylcholine release, and via inhibition of acetylcholinesterase (AChE) activity in the stomach. Acotiamide enhances the effects of ACh release from nerve terminals of the enteric nervous system presumably via a combination of reversible inhibition AChE and antagonism of the inhibitory presynaptic M1 and possibly M2 receptors. Thereby it increases the availability of ACh on postsynaptic receptors in the enteric nervous system and at the neuromuscular junction. In addition, acotiamide itself may act on a postsynaptic M5-like ACh receptors, accentuating rhythmic smooth muscle contractions through an agonistic effect. Furthermore, enhanced gastric accommodation to meal ingestion has been shown after acotiamide treatment. Acotiamide may also modify brain–gut interactions via its effects on the afferent vagus nerve, modifying sensory input from the GI tract to the CNS or modulating vago–vagal reflex pathways. All of these effects on gastrointestinal motility provide the drug with an attractive pharmacodynamic profile for the treatment of FD with PDS which is at least in part associated with delayed gastric emptying, impaired gastric accommodation and susceptibility to anxiety and stress [3] The gastroprokinetic activity of acotiamide does not appear to be associated with prolongation of the QT interval, based on animal study. In this study, unlike cisapride, acotiamide had no effects on myocardial monophasic action potential duration, QT interval or corrected QT interval [4].

Pharmacokinetics

After oral intake, maximum plasma levels of acotiamide are reached 1–1.5 h after ingestion. The drug has a plasma half-life of 7–10 h. On average, 45% of acotiamide is excreted in the faeces. Acotiamide has no signfiicant inhibitory effect on cytochrome P450

Clinical Studies

The effect of acotiamide 100 mg three-times a day (t.i.d) before meals was studied in a subject group comprised of healthy controls and FD patients (n = 57; HC: 27, FD: 30) [5]. In a randomized, double-blind, placebo-controlled, cross-over design, both healthy controls and FD patients were administered acotiamide or placebo during two treatment periods (7–9 days) separated by a 2 week wash-out period. At the end of each treatment period, a standard nutrient challenge test was performed. Global symptom assessment of FD patients during a nutrient challenge did not yield statistically significant results while there was a trend in favor of acotiamide (23% for placebo, 35% for acotiamide). Indeed, individual symptom assessment revealed significantly decreased bloating and belching scores.

Gastric emptying in functional dyspepsia patients tended to be faster on treatment while acotiamide did not enhance gastric emptying in healthy controls (FD; placebo: 166 ± 100 min; acotiamide: 144 ± 58 min; HC; placebo: 135 ± 52 min; acotiamide: 143 ± 46 min) [6].

Another study utilized gastric ultrasound to measure the crosssectional area of the proximal stomach after a liquid meal to assess gastric accommodation in FD patients before and after

treatment with acotiamide 100 mg t.i.d [7]. The study also evaluated gastric emptying rate, motility index and duodeno-gastric reflux index for assessment of gastroduodenal motility. A significant difference was found in the percentage change of gastric accommodation between the acotiamide group and the placebo group (21.7 vs 4.4%). Furthermore, acotiamide was found to significantly accelerate the gastric emptying rate without a corresponding acceleration in the placebo group. The subjective improvement rates also tended to be better in the acotiamide group (31.6 vs 16.7%)[8]. Neither of these studies reports serious adverse effect and change in ECG during or after acotiamide treatment.

In a multicenter, randomized, placebo-controlled, parallel-group, Phase III trial in Japan, FD patients were recruited based on modified Rome II criteria, making them very similar to the PDS subgroup according to Rome III criteria [9,10,11]. Patients were required to have at least one of four symptoms (upper abdominal pain, upper abdominal discomfort, epigastric pain or epigastric burning) for at least 6 months before inclusion. Patients were asked to record individual symptoms on a severity scale of 0–3, weekly overall treatment scores (comparing pretreatment symptoms during the baseline period with the current symptoms) on a 7-point Likert scale ranging from 'extremely improved' to 'extremely aggravated' and Quality of Life questionnaires; the Japanese version of Short Form-Nepean Dyspepsia Index questionnaire was used at baseline, at week 4 of treatment, and week 4 of the post-treatment follow-up period. The study was designed to have an 8-day baseline period, a 4-week treatment period and a 4-week post-treatment follow-up period. The two coprimary end points were overall treatment efficacy (OTE) and elimination rate (no symptoms) of all three cardinal symptoms (postprandial fullness, upper abdominal bloating and early satiation at the last survey). Patients who filled out 'extremely improved' or 'improved' on the OTE were considered responders. Eight hundred and ninety seven patients were randomly assigned to receive one of the two trial drugs: 100 mg of acotiamide (452 patients) or placebo (445 patients) t.i.d. The responder rate based on the OTE at the last survey point was 52.2% with acotiamide and 34.8% with placebo ($p < 0.001$). This improvement of OTE scores was already present and statistically significant during week 2 of treatment. The significant benefit with acotiamide persisted during weeks 3 and 4 and, interestingly and unprecedented, persisted in approxminately 50% of patients throughout the follow-up period after the completion of trial drug administration. The elimination rate of all three meal-related symptoms at the last survey point was 15.3% with acotiamide and 9.0% with placebo ($p = 0.004$). Significantly, higher elimination rates for individual symptoms occurred in the acotiamide group compared with placebo; for postprandial fullness (22.7 vs 16.6%; $p = 0.026$); and for early satiation (37.8 vs 25.4%; $p < 0.001$). The responder rates (more than 50% decrease in symptom severity) for postprandial fullness, early satiation, upper abdominal pain and upper abdominal bloating were significantly higher during acotiamide treatment as compared with placebo. The number needed to treat for OTE was six, and for symptom elimination, it was 16. No serious treatment-related adverse effects were reported in this study. There was no significant difference between any of the most common side effects (elevation of serum triglycerides, serum prolactin or serum gamma-glutamyltransferase, and nasopharyngitis) between placebo and acotiamide groups. The Phase III trial was followed by a multicenter, open-label, single-arm, long-term (48 weeks) study with acotiamide 100 mg t.i.d. in Japan in patients closely corresponding to PDS patients according to the Rome III consensus [12]. Patients were required to have at least one of the four symptoms (upper abdominal pain, upper abdominal discomfort, epigastric pain or epigastric burning) for at least 6 months before inclusion.

The 48-week trial was preceded by an 8-day baseline period. Similar to the Phase III study, patients were asked to rate nine symptoms (upper abdominal pain, upper abdominal discomfort, postprandial fullness, upper abdominal bloating, early satiation, excessive belching, nausea, vomiting and heartburn) on a severity scale of 0–3 (none, mild, moderate and severe) daily during the 8-day baseline period and until the first 8 weeks in the treatment period. Patients also completed a weekly global assessment of an OTE questionnaire.

Trial medication was administered to 409 patients of which 405 were eligible for statistical efficacy analysis. Based on the cessation criterion (responder for 3 consecutive weeks), initial dosing was interrupted in 304 patients (75.1%). Based on the relapse criterion (nonresponse during 2 consecutive weeks off therapy), treatment was resumed in 167 of these 304 patients. A total of 154 (38 %) patients achieved remission (dose interruption without relapse for 12 weeks) after a mean treatment duration of 60.6 days. Treatment response was evaluated over the course of the 48-week study (with decreasing numbers of patients still under therapy over time). The OTE improvement rate was 26.1% at week 1 and 48.9% at week 4. It continued to increase and reached 60.6% at week 8 and stabilized thereafter around 60% for the remainder of the study. Only one serious adverse effect was observed: increased alanine aminotransferase in one patient. Most of the other side effects were mild. The high number of patients who achieved sustained remission, the high rate of OTE improvement and the rarity of adverse effects are noteworthy in this extension trial.

Safety

In clinical studies, the incidence of adverse events was comparable between Acotiamide and placebo. The most common adverse reactions reported are diarrhoea (2.1%), constipation (1.6%), nausea (0.8%), and vomiting (0.5%).

Summary & conclusions

Acotiamide, a new first-in-class oral prokinetic drug, is an upper gastrointestinal motility modulator for the treatment of abdominal symptoms in FD. Exploratory studies with acotiamide confirmed its ability to decrease gastric emptying time in patients. A European study was indicative of enhanced gastric accommodation with acotiamide treatment In the Phase II studies, acotiamide 100 mg t.i.d showed the most consistent evidence of therapeutic benefit. The results of the recent placebo-controlled Phase III trial in Japan revealed significantly higher OTE response, higher elimination rate in three cardinal symptoms of PDS (postprandial fullness, upper abdominal bloating and early satiety) and significantly improved quality of life with acotiamide 100 mg t.i.d. compared with placebo. Finally, in a long-term (48 week) open-label trial, a favorable clinical course with acotiamide 100 mg t.i.d was demonstrated.

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