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Updates in Gastroenterology: Acotiamide for Treatment of Functional Dyspepsia

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Commentary
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Abstract

Functional dyspepsia (FD) comprises of two types, the postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS). Acotiamide is a new prokinetic agent that acts by increased release of acetylcholine and is used in the treatment of FD-postprandial distress syndrome (FD-PDS). The drug initially launched in Japan is the world's first approved treatment for FD. It exerts its activity via muscarinic receptor inhibition, which enhances acetylcholine (ACh) release, and via inhibition of acetylcholinesterase (AChE) activity in the stomach. It increases the availability of ACh on postsynaptic receptors in the enteric nervous system. The gastroprokinetic activity of acotiamide does not cause prolongation of the QT interval. Long-term studies of 48 weeks have shown a favorable clinical course with acotiamide in FD.

Keywords: Functional Dyspepsia; Acetylcholine; Acotiamide; Prokinetic

Abbreviations: FD: Functional Dyspepsia; PDS: Postprandial Distress Syndrome; EPS: Epigastric Pain Syndrome; FD-PDS: FD-postprandial Distress Syndrome; Ach: Acetylcholine; AChE: Acetyl Cholinesterase.

Introduction

Functional dyspepsia is a prevalent upper gastrointestinal condition with major morbidity. It is defined as the presence of one or more bothersome symptoms (postprandial fullness [PPF], early satiation [ES], epigastric pain, epigastric burning) that are unexplained after a clinical evaluation. FD comprises of two types, the postprandial distress syndrome (PDS), which is associated with meal-induced dyspeptic symptoms, and epigastric pain syndrome (EPS), which refers to epigastric pain or epigastric burning that does not occur exclusively postprandially. Of patients with functional dyspepsia, approximately 38% are postprandial distress syndrome, 27% are epigastric pain syndrome, and 35% meet criteria for both [1].

Acotiamide is a new prokinetic agent that acts by increased release of acetylcholine and is used in the treatment of FD-postprandial distress syndrome (FD-PDS). Its mode of action is unrelated to dopamine D2 or serotonin receptor activity, for which the drug exhibits very low affinity. The drug was approved and launched in Japan in June 2013, making it the world's first approved treatment for FD. The drug has initiated the approval process in North America and European countries [2].

Pharmacology

Mechanism

It exerts its activity via muscarinic receptor inhibition, which enhances acetylcholine release, and via inhibition

of acetylcholinesterase (AChE) activity in the stomach. Acotiamide accentuates the effects of ACh release from nerve terminals by a reversible inhibition AChE and antagonism of the presynaptic M1 and possibly M2 receptors. Therefore, it increases the availability of ACh on postsynaptic receptors in the enteric nervous system and at the neuromuscular junction.

Acotiamide has shown to modify brain–gut interactions via its effects on the vagus nerve, altering the sensory inputs from the GI tract to the CNS or modulating vago–vagal reflex pathways. The gastroprokinetic activity of acotiamide does not cause prolongation of the QT interval. Unlike cisapride, acotiamide had no effects on myocardial monophasic action potential duration, QT interval or corrected QT interval [3].

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 [4].

Clinical Trials

In a Phase III Randomized Clinical Trial, on 220 patients with active PDS were centrally randomized either 100 mg Acotiamide or 5 mg Mosapride TID for 4 weeks [5].

Study Design

This multicenter, randomized, active-controlled, parallel-group, assessor blind, phase 3 study was designed to evaluate the efficacy and safety of Acotiamide in comparison with Mosapride in patients with FD-PDS.

Patients of either gender aged ≥18 years to ≤64 years and diagnosed with FD-PDS as per the Rome III classification were included in the study.

Inclusion and Exclusion Criteria

Patients with a history of heartburn within 12 weeks; diabetes mellitus requiring treatment; presence of any clinically significant metabolic, hepatic, renal, or hematological disorders; and drug or alcohol abuse were excluded. After the baseline period, anti-secretory drugs, prokinetics, antacids, non-steroidal anti-inflammatory drugs, and antidepressant drugs were not allowed.

The results demonstrated that Acotiamide is efficacious, well-tolerated and had significantly improved the QoL over a 4-week treatment period in these patients. The efficacy and tolerability of Acotiamide were similar to Mosapride.

The effect of acotiamide 100 mg t.i.d before meals was evaluated in a subject group comprised of healthy controls and FD patients (n = 57; HC: 27, FD: 30) [6]. 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. Symptom assessment 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). There were significantly decreased bloating and belching scores.

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%). A long-term safety trial is the first to demonstrate that acotiamide can safely be administered continuously for 1 year [7].

Conclusion

To summarize, Acotiamide, a new first-in-class oral prokinetic drug, is useful for the treatment of abdominal symptoms in FD. Exploratory studies with acotiamide confirmed its ability to decrease gastric emptying time in patients. Long term studies of 48 weeks have shown a favorable clinical course with acotiamide 100 mg t.i.d.

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