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Modern Possibilities of Using Acotiamide in the Treatment of Functional Dyspepsia

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Aim: to evaluate the efficacy and safety of the new prokinetic drug acotiamide in the treatment of functional dyspepsia.
Key findings. Acotiamide is an antagonist of inhibitory muscarinic receptors of type 1 and 2 and a reversible inhibitor of acetylcholinesterase activity. In patients with functional dyspepsia acotiamide normalizes the accommodation of the fundal part of the stomach and accelerates delayed gastric emptying. The conducted studies have confirmed the higher efficacy of acotiamide compared to placebo in reducing the severity of such symptoms of functional dyspepsia as a feeling of epigastric postprandial fullness and bloating, early satiation. The advantage of acotiamide in comparison to other prokinetics (in particular, metoclopramide and domperidone) is the high safety of use and the absence of influence on the duration of the Q-T interval.
Conclusion. The high efficacy and safety of the application makes it advisable to use acotiamide in the treatment of patients with functional dyspepsia.
Keywords: functional dyspepsia, prokinetics, acotiamide
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Современные возможности применения акотиамида в лечении функциональной диспепсии

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Цель обзора. Оценить эффективность и безопасность применения нового прокинетического препарата акотиамида при лечении функциональной диспепсии.
Основные положения. Акотиамид является антагонистом ингибиторных мускариновых рецепторов 1-го и 2-го типа и обратимым ингибитором активности ацетилхолинэстеразы. У пациентов с функциональной диспепсией акотиамид нормализует аккомодацию фундального отдела желудка и ускоряет замедленное опорожнение желудка. Проведенные исследования подтвердили более высокую эффективность акотиамида по сравнению с плацебо в уменьшении выраженности таких симптомов функциональной диспепсии, как чувство переполнения и вздутия в подложечной области после еды, раннее насыщение. Преимуществом акотиамида по сравнению с другими прокинетиками (в частности, метоклопрамидом и домперидоном) является высокая безопасность применения и отсутствие влияния на продолжительность интервала Q-T.
Заключение. Высокая эффективность и безопасность применения делает целесообразным использование акотиамида в лечении больных с функциональной диспепсией.
Ключевые слова: функциональная диспепсия, лечение, акотиамид
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Based on the revised Rome IV criteria, functional dyspepsia (FD) is understood as a set of symptoms (epigastric pain and burning, postprandial fullness and bloating, early satiety) that have been observed in a patient for the last 3 months (with their total duration of at least 6 months) and which cannot be accounted for by organic disorders (such as peptic ulcer, chronic pancreatitis, etc.). Depending on FD symptoms which come to the fore in clinical presentation, one distinguishes between epigastric pain syndrome (EPS), where the leading complaints are epigastric pain and burning, and postprandial distress syndrome (PPDS), where the prevailing complaints include postprandial fullness, bloating, and early satiety. Both variants of FD may be combined with each other, as well as with belching and nausea [1].

The relevance of the issue of FD is primarily due to the fact that it is one of the most common gastrointestinal diseases. Its prevalence in the USA, Canada and the UK is 8–12 % [1]. In particular, PPDS accounts for 61 % of FD cases, EPS accounts for 18 %, and the combination of both variants occurs in 21 % of patients [2]. The quality of life in patients with FD is significantly decreased. They are more likely to take sick leave compared to other employees, while their examination and treatment is associated with higher healthcare expenditures [3].

The choice of medications for the treatment of patients with FD depends on its clinical variant. The revised Rome IV criteria recommend the administration of antisecretory drugs for EPS: histamine H_2-receptor blockers, proton pump inhibitors (PPIs), which, according to controlled studies, are 10–15 % more effective than placebo. The use of antisecretory drugs for PPDS has little success. Such cases require drugs that normalise the motility of the upper gastrointestinal tract [1]. The objective of this review is to assess the efficacy and safety of the new prokinetic drug acotiamide.

Pharmacological properties and mechanisms of action of acotiamide

Acotiamide (acotiamide hydrochloride trihydrate or Z-338), which is fully referred to as N-[2-[bis(1-methylethyl)amino]ethyl]-2-[(2-hydroxy-4,5-dimethoxybenzoyl)amino]thiazole-4-carboxamide, is an antagonist of inhibitory muscarinic type 1 and type 2 receptors and has a relative molecular weight of 450.6 g/mol [4]. The inhibition constant (K_i) of acotiamide in respect of human M_1- and M_2-muscarinic receptors is 27 and 31 μmol/L, respectively, so that acotiamide can produce its pharmacodynamic effects.

What is more, acotiamide also has a reversible inhibitory effect on the activity of acetylcholinesterase (AChE). The median inhibitory concentration (IC_{50}) of acotiamide regarding human AChE is 3 μmol/L. The prokinetic effect of acotiamide is completely eliminated after preliminary administration of atropine. Unlike metoclopramide, domperidone and mosapride, acotiamide does not show affinity for D_2-dopamine and serotonin receptors [5, 6].

The interaction of acotiamide with M_1- and M_2-muscarinic acetylcholine receptors and the inhibition of AChE in patients with FD normalises accommodation of the stomach fundus and accelerates its delayed emptying [7–9]. It is noteworthy that when the gastric evacuation function was assessed using a ^{13}C-breath test with acetic acid in healthy volunteers, acotiamide at a dose of 100 and 300 mg before meals did not affect the evacuation of liquid food [10, 11].

Efficacy of acotiamide in the treatment of patients with functional dyspepsia

K. Matsueda et al. [12] conducted a multicenter Japanese study that included 892 patients, of which 450 patients received acotiamide 100 mg 3 times daily for 4 weeks, and 442 patients received placebo. The study assessed the overall treatment effect and the rate of elimination of symptoms associated with eating (epigastric fullness after eating, epigastric bloating, early satiety). The assessment was carried out using the Likert scale that contained 7 variations of changes in clinical symptoms as compared to baseline: “marked improvement”, “improvement”, “slight improvement”, “no changes”, “slight deterioration”, “deterioration”, and “marked deterioration”.

Overall treatment effect in this study was noted in 52.2 % of the patients treated with acotiamide and in 34.8 % of the patients treated with placebo ($p < 0.001$). After 4 weeks of treatment, the disappearance of all the three symptoms associated with eating was noted in 15.3 % of the patients treated with acotiamide and 9.0 % of the patients treated with placebo ($p = 0.004$). Epigastric fullness after eating disappeared in the groups of patients receiving acotiamide and placebo in 22.7 and 16.6 % of cases, respectively ($p = 0.026$), epigastric bloating — in 34.5 and 28.5 % ($p = 0.084$), early satiety — in 25.4 and 37.8 % of the cases ($p < 0.001$). At the same time, the quality of life of patients in the main group was significantly improved as compared to that in the group of patients treated with placebo. The rate of adverse effects in the main group and control group was the same, while no significant cardiovascular effects were detected.

S. Shinozaki et al. [13] observed 33 patients with EPS and 41 patients with PPDS who received acotiamide at a dose of 100 mg 3 times daily

for 3 months. After 1 month of treatment in the group of patients with EPS, an improvement was noted in 63 % of the patients, the complete disappearance of complaints — in 42 % of the patients. At 3 months of treatment, the rates were 69 and 39 %, respectively. In the group of patients with PPDS, the severity of complaints decreased after a month in 56 % of the patients, after 3 months — in 78 % of the patients ($p = 0.021$). The complete disappearance of complaints was noted after a month in 17 % of the patients, after 3 months — in 46 % of the patients ($p = 0.004$). The treatment effect was lower in severe FD ($p = 0.013$). The authors concluded that acotiamide is effective for both EPS and PPDS.

S. Porika et al. [14] observed 132 Indian patients (85 men and 47 women) with FD who received acotiamide at a dose of 100 mg 3 times daily during 4 weeks. At the end of weeks 2 and 4, the Likert scale was used to evaluate the overall treatment effect on PPDS, EPS and concomitant symptoms (nausea, vomiting, belching), as well as the quality of life.

The efficacy of acotiamide after 2 and 4 weeks of treatment was 51.5 and 65.9 %, respectively, in the patients with PPDS, 31.8 and 41.7 % — in the patients with EPS. The disappearance of nausea, vomiting and belching after 2 weeks was observed, respectively, in 18.2 %, 17.4 % and 16.7 % of the patients, after 4 weeks — in 18.2 %, 17.4 % and 18.2 %. The quality of life in these patients was also significantly improved. Adverse effects were detected only in 7 patients (5.3 %), while dizziness was noted in 4 people, headache — in 3, nausea — in 1.

K. Matsueda et al. [15] conducted a comparative study of the most effective daily dose of acotiamide in the treatment of FD [15]. Within 4 weeks, 115 patients with FD received acotiamide at a dose of 50 mg 3 times daily, 108 patients — at a dose of 100 mg 3 times daily, 116 people — at a dose of 300 mg 3 times daily, and 112 patients received placebo. The overall treatment effect was assessed using the Likert scale.

A decrease in the severity of FD symptoms was observed in 49.1 % of the patients taking placebo, in 48.7 % of the patients taking acotiamide at a daily dose of 150 mg, in 58.3 % of the patients receiving acotiamide at a daily dose of 300 mg, and in 56.9 % of the patients taking acotiamide at a daily dose of 900 mg. In the patients taking acotiamide at a dose of 100 mg 3 times daily, the rate of elimination of abdominal fullness after eating was significantly higher than in the patients taking placebo. The authors concluded that the stated product dose is most effective in the treatment of FD.

A meta-analysis of 6 studies showed that the probability of a decrease in the severity of FD symptoms (hazard ratio, HR) in the patients receiving acotiamide compared to the patients taking placebo was 1.29 ($p < 0.00001$). Acotiamide was effective in the patients with PPDS (HR = 1.29; $p = 0.003$), but its effect on EPS did not differ from that of placebo (HR = 0.92; $p = 0.39$). The rate of adverse effects was not different in the groups of patients receiving acotiamide and placebo. The most effective dose was 100 mg 3 times daily [16].

Another endpoint was the rate of recurrent FD symptoms after discontinuation of acotiamide. S. Shinozaki et al. [17] showed that by the end of the year after the treatment discontinuation, disease remission persisted in 51 % of the patients. It was found that the presence of a mixed variant of FD (a combination of EPS and PPDS) in patients is a predictor of recurrence. Re-initiation of therapy with acotiamide led to a decrease in the severity of clinical symptoms of the disease by the end of the first month. In another study, these authors observed 79 patients with FD (for an average of 1.9 years) after successful treatment with acotiamide. Recurrent clinical symptoms of the disease were noted in 25 % of the patients. They were most common in patients with a very pronounced clinical pattern of PD (the odds ratio (OR) was 15.04; $p = 0.013$). Continued administration of acotiamide during the year significantly reduced the rate of recurrences (OR = 0.16; $p = 0.004$) [18].

As is known, FD often goes together with gastroesophageal reflux disease (GERD), which is caused by an increase in the rate of spontaneous relaxation of the lower esophageal sphincter associated with impaired accommodation of the stomach fundus [3]. K. Muta et al. [19] observed 29 patients with FD who simultaneously presented clinical symptoms associated with gastroesophageal reflux. The patients took acotiamide at a dose of 100 mg 3 times daily for 2 weeks. After the treatment, the severity of the clinical symptoms associated with both FD and GERD in the patients was decreased. Y. Funaki [20] conducted a double-blind, placebo-controlled study that included 16 patients with FD, who also presented heartburn associated with non-erosive GERD and were resistant to the use of PPIs. The addition of acotiamide reduced not only the feeling of epigastric fullness after eating, but also the severity of heartburn.

A number of studies was conducted to assess the efficacy of concomitant use of acotiamide and antisecretory drugs (PPIs, H_2-histamine receptor blockers). Thus, it was shown that concomitant use of acotiamide (at a dose of 300 mg/day) and rabeprazole (at a daily dose of 10 mg) significantly

reduced the severity of complaints both in the patients with EPS and in the patients with PPDS [21]. S. Mayanagi et al. [22] used acotiamide at a dose of 100 mg 3 times daily in patients with FD, who did not sufficiently benefit from monotherapy with esomeprazole at a dose of 20 mg/day. After 2 weeks of concomitant therapy, 78 % of the patients had a decrease in the severity of both EPS symptoms and PPDS symptoms.

T. Takeuchi et al. [23] conducted a study that included patients with a combination of FD and GERD, who did not sufficiently benefit from rabeprazole monotherapy that had been carried out for 8 weeks. The patients were randomised into two groups: the patients in Group 1 were treated with acotiamide at a dose of 100 mg 3 times daily, the patients in Group 2 received a double dose of rabeprazole. A decrease in the severity of such symptoms as heartburn, epigastric pain, and a feeling of epigastric fullness by more than 50 % was noted in Group 1 in 40.8 % of the patients, in Group 2 — in 46.9 % of the patients (the differences are non-significant). The authors concluded that in the case of patients resistant to a combination of FD and GERD to rabeprazole, the combination of acotiamide and rabeprazole may be an alternative to a double dose of PPIs.

M. Hojo et al. [24] conducted a randomised, controlled, comparative study to assess efficacy of the concomitant use of acotiamide (100 mg 3 times daily) and famotidine (10 mg 2 times daily), as well as a combination of acotiamide and placebo in 50 patients with FD (25 people in each group) for 28 days. A performed analysis of the overall treatment effect revealed no significant differences between the groups, however, the number of patients with EPS, whose pain severity scores decreased by more than 50 % compared to the baseline in the group of patients receiving acotiamide and famotidine was higher than in the group of patients receiving placebo.

Comparative efficacy and safety of using acotiamide and other prokinetics

A number of studies were conducted to compare the efficacy of acotiamide and other prokinetics. Thus, S. Sinha [25] conducted a comparative study that included 220 patients with PPDS who took either acotiamide at a dose of 100 mg 3 times daily or the prokinetic mosapride at a dose of 5 mg 3 times daily during 4 weeks. The overall treatment effect in the intention-to-treat (ITT) population was 95.15 % for acotiamide, 89.81 % — for mosapride, in the per protocol analysis — 98 and 93.3 %, respectively. Both agents were well tolerated. The authors concluded that both agents were equally effective.

Y. Yang et al. [26] performed a meta-analysis of 25 randomised controlled studies involving a total of 4473 patients with FD. Assessment of the results involved calculation of the odds ratio (OR). Thus, the efficacy of acotiamide and itopride turned out to be similar (OR = 1.1). The efficacy of acotiamide as compared to domperidone (OR = 1.51), trimebutine (OR = 2.32) and metoclopramide (OR = 3.07) was lower.

At the same time, there is an acute issue of the safety of using prokinetics (first of all, metoclopramide and domperidone). The most common adverse effects of metoclopramide, which is an agonist of type 4 serotonin receptors, as well as an antagonist of central and peripheral type 2 dopamine receptors, include extrapyramidal disorders, central nervous system effects, and hyperprolactinemia.

With the use of the antagonist of peripheral type 2 dopamine receptors domperidone, these adverse effects are less common and less severe. Domperidone, in turn, was able to block the hERG (IKr) potassium channels of the cardiac conduction system, to prolongate the ventricular repolarisation phase and to increase the QT interval duration with a risk of developing serious rhythm disorders. This complication is also typical of serotonin receptor agonists (cisapride, mosapride, prucalopride) [27].

Unlike the stated agents, acotiamide has no effect on type 2 dopamine receptors and does not affect the QT interval duration [5]. It was shown that the rate of adverse effects, such as increased levels of prolactin, alanine aminotransferase and bilirubin in the blood of FD patients treated with acotiamide and placebo was not different [28]. The high safety profile of acotiamide used to treat FD was also noted by other authors [7].

Since patients with FD are often concomitantly infected by *Helicobacter pylori* (*H. pylori*), the possible effect of acotiamide therapy on the results of testing for this infection was of interest. It was found that the use of acotiamide at a dose of 100 mg 3 times daily did not affect the findings of the ^{13}C-urease breath test for *H. pylori* [29].

Given the efficacy and safety of acotiamide, the guidelines of the Japanese and British Societies of Gastroenterology consider it as a first-line treatment of FD [30, 31]. The guidelines of the Russian Gastroenterological Association for the diagnosis and treatment of FD also contain information about this agent [32]. The proposed authorisation of acotiamide in Russia will make its use possible in our country as well.

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