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TREATMENT OF FUNCTIONAL GASTROINTESTINAL DYSPEPSIA

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ABSTARCT

Prokinetic drugs (prokinetics) are drugs that enhance and coordinate muscle contractions of the gastrointestinal (GI) tract, including coordination between different intestinal segments, thereby increasing the movement of intraluminal contents. The review considers modern approaches to the use of prokinetics in the treatment of motor disorders of the gastrointestinal tract. The results of studies of various classes of drugs that have a prokinetic effect and target various pathophysiological mechanisms, including impaired antroduodenal coordination, manifested by subjective symptoms and an objective delay in gastric emptying, are presented. Currently used in clinical practice and registered in Uzbekistan, the drug domperidone still remains relevant: in the treatment of patients with functional dyspepsia, gastroparesis and gastroesophageal reflux disease, it is recommended to take it in combination with proton pump inhibitors. Domperidone has an antiemetic effect and a favorable safety profile when used for its registered indications.

Keywords: functional dyspepsia, gastroesophageal reflux disease, gastroparesis, prokinetics, delayed gastric emptying, antroduodenal coordination, antiemetic effect.

Introduction

Prokinetic drugs (prokinetics) are drugs that enhance and coordinate muscle contractions of the gastrointestinal tract (GIT), including coordination between different segments of the intestine, thereby enhancing the movement of intraluminal contents [1]. Prokinetics show pharmacological activity in the selective areas of the gastrointestinal tract, which is determined by the location of receptor targets for their pharmacological action.

Types of gastric motility disorders. There are three predominant motor dysfunctions that can lead to different manifestations or symptoms in patients with functional dyspepsia: delayed gastric emptying, gastric accommodation dysfunction, and pyloric dysfunction. Symptoms associated with delayed gastric emptying are nausea, vomiting, and bloating in the upper abdomen, with pain not being a typical symptom of delayed gastric emptying [2]. Gastric accommodation disorders are usually associated with postprandial distress syndrome, a component of functional dyspepsia. Thus, among patients with clinical symptoms of postprandial distress syndrome, about 25% have a delay in emptying the stomach, about 25% have a violation of the accommodation of the stomach and about 25% have a combination of these motor dysfunctions [3].

Detection of gastric emptying disorders requires an accurate test. Currently, there are three direct and one indirect measurement of stomach accommodation. Three direct methods include: single-photon emission computed tomography, measurement of the proximal volume of the stomach using a barostat (for which the air pressure inside the pliable polyethylene cylinder is pumped and maintained constant using an electronic pump that sucks or pumps air, and continuous monitoring of the volume inside the balloon provides measurement of the volume of

the stomach) [4], high-resolution intraluminal manometry in the proximal part of the stomach [5]. Indirect measurement of stomach accommodation occurs by taking a nutritious drink at a constant rate of its intake until reaching the maximum permissible, this method allows you to assess the sensation in the stomach [6]. The use of this method also makes it possible to indirectly assess the accommodation of the stomach if the caloric content of the drink is less than 750 kcal, since there is a linear correlation between the use of this method and the amount of accommodation of the stomach measured by the barostat, with the caloric content of liquid food below 750 kcal [6]. Attempts have been made to use two-dimensional visualization of the proximal region of the stomach immediately after a meal to assess the accommodation of the stomach, but it was subsequently found that these measurements are inaccurate compared to the three-dimensional image, and therefore the 2D imaging method requires further validation [7]. The relationship between the acceleration of gastric emptying and the improvement of symptoms with the use of domperidone has been demonstrated [2]. Gastric emptying disorders can be reduced by targeting specific receptors, including serotonergic 5-HT_4, as well as dopamine$_{D2/3}$ receptors and neurokinin 1 (NK1) receptors [8]. In fact, approaches to improving postprandial accommodation have been associated with reduced symptoms of functional dyspepsia, such as using the serotonergic agonist 5-HT_{1A} buspirone, or using acothiamide, an acetylcholinesterase antagonist and a presynaptic M1 and M2 antagonist of muscarinic receptors [8]. These muscarinic receptors are involved in inhibiting the release of acetylcholine. Consequently, being an antagonist of these receptors and inhibiting acetylcholinesterase, acothiamide leads to an increase in local levels of acetylcholine, which is a stimulating transmitter in the enteric nervous system and parasympathetic nerve pathways [9].

Pyloric dysfunction is difficult to assess non-invasively, and two approaches are currently available that require intraluminal measurements. These are anthropylogenous manometry and the use of the Endoflip device (endoscopic functional probe for imaging the lumen of the stomach). When conducting anthropylodiudenal manometry, closely spaced gauges are used to measure pressure and the activity of the gatekeeper is determined by a combination of phase and tonic contractions, as well as by a combination of antral and duodenal phase pressure activity during manometric tracking [10].

Several "new generation" 5-HT 4-receptor agonists are selective for 5-HT_4 receptors without the risk of side effects, these include prucalopride, velusetrag, naronapride and felcisetrag [12] (the last three drugs are not registered in the Russian Federation). Prucalopride is approved by the European Medicines Agency (EMA) and the Food and Drug Administration (U.S. Food and Drug Administration). Administration, FDA) for the treatment of chronic constipation. In a randomized placebo-controlled crossover study involving 34 patients with motor disorders of the upper gastrointestinal tract (28 c idiopathic, 6 with diabetic gastroparesis), some of them received prucalopride 2 mg 1 r / day, some - placebo for 4 weeks. with a 2-week laundering period. Prucalopride was effective in alleviating the symptoms caused by general gastroparesis by the cardinal symptoms index of the subscal of nausea/vomiting, satiety/satiety, and bloating, while also improving the overall assessment of patients' quality of life [13]. Similarly, the effectiveness of velusetrag has been shown in the treatment of patients with diabetic and idiopathic gastroparesis [14]. Intravenous felcisetrag was accompanied by a significant acceleration of gastric emptying, small intestine transit and colon emptying compared with

placebo use in patients with gastroparesis and previously confirmed delayed gastric emptying; at the same time, the drug was well tolerated [15]. In a randomized trial [16] in two parallel groups, the drug felcisetrag (TAK-954), administered to patients on mechanical ventilation and with intolerance to enteral nutrition, defined as the residual volume of the stomach ≥200 ml, led to an increase in the proportion of patients with normal gastric emptying compared with metoclopramide prescribed at 10 mg 4 r / day. Velusetrag and felcisetrag (TAK-954) did not have a significant effect on the tone of the coronary vessels according to pharmacological studies. In addition, these drugs did not have a negative effect on heart rhythm and platelet function [17]. Felcisetrag has a high affinity (pK_i 9,4) for human recombinant 5-HT_4 receptors with more than 2000-fold selectivity for these receptors [18].

Another potential mechanism for enhancing the neuromuscular function of the stomach is the anti-inflammatory effect, which may contribute to the stimulation of the vagus nerve. This was demonstrated with a 5-HT_4 prucalopride agonist that modified the T cell response of 2-helper cells and reduced the intensity of the developed postoperative intestinal obstruction [19].

In disorders of the upper gastrointestinal tract associated with increased sensitivity of the stomach, such as functional dyspepsia, dopaminergic antagonist $D_{2/3}$ trazpyrobene (TAK-506) (not registered in the RF) was taken as a nutritious drink for 1 week, which led to a significant increase in stomach volume compared to baseline [20]. Moreover, in a placebo-controlled study [21], the appointment of an antagonist of the NK1 aprepitant receptor was accompanied by an improvement in the antagonist of the NK1 receptor. clinical symptoms of gastroparesis, including nausea. This effect may reflect the known effect of NK1 receptor antagonists on the vomiting center in the brainstem, similar to the effect associated with reducing chemotherapy-induced vomiting. Another potential mechanism of symptomatic effect may be associated with an increase in fasting stomach volume and accommodation without negatively affecting gastric emptying, which was demonstrated in a study involving healthy volunteers [22]. As shown by the results of a randomized controlled trial [23], the use of a new antagonist of the NK1 receptor - a tradipitant (not registered in the Russian Federation) was accompanied by an improvement in the symptoms of gastroparesis within 4 weeks.

Another promising direction for improving gastric motility is the use of ghrelin receptor agonists. Ghrelin consists of 28 amino acids, is mainly localized in the stomach, stimulates appetite. The administration of a pharmacological dose of recombinant human ghrelin increased the tone of the proximal part of the stomach due to central and peripheral effects [24], and in some studies it also accelerated gastric emptying in patients with gastroparesis [25]. Synthetic pentapeptide, a ghrelin receptor agonist (RM-131), has 130 times more potent action than natural ghrelin [26, 27]. The ghrelin receptor agonist relamorelin increases the frequency of distal antral contractions without interfering with stomach accommodation or altering satiety after meals in healthy volunteers, which distinguishes its action from that of the macrolide antibiotic erythromycin [28].

One of the most studied drugs with prokinetic action are motilin receptor agonists. These include macrolide antibiotics, which stimulate gastrointestinal motilene receptors (especially gastric receptors). Erythromycin improves gastric emptying and temporarily improves symptoms before the motilin receptor is suppressed (approximately 4 weeks after the start of therapy), which is noticeable by the appearance of tachyphylaxis or a decrease in the

effectiveness of treatment [29]. One of the appealing aspects of erythromycin is that it stimulates fundal and antral contractions while suppressing the contractility of the pylorus [30]. The current recommended dose for hospitalized patients with gastroparesis is 1.5–3.0 mg/kg (intravenous infusion for 45 min) every 6–8 hours, for outpatient treatment of gastroparesis, 125 mg orally for several weeks is recommended. Side effects that occur with erythromycin treatment include abdominal pain, nausea, and diarrhea. The greatest caution should be exercised when using erythromycin concomitantly with drugs that are metabolized with the participation of the cytochrome P450 isoenzyme (CYP) 3A4 (for example, diltiazem, verapamil or domperidone), since drug interactions can cause sudden cardiac death [31].

One of the promising areas of prokinetic therapy is the impact on the bottom of the stomach. Studies have shown that the use of akothiamide improves the accommodation and emptying of the stomach after taking liquid food [32] and improves symptoms in patients with functional dyspepsia [33]. The use of some 5-HT_4 receptor agonists, such as tegaserode (not registered in the Russian Federation), in patients with functional dyspepsia with normal gastric emptying was also accompanied by increased accommodation of the stomach [34]. This serves as a justification for their use in functional dyspepsia. In a study using simultaneous measurement of gastric accommodation and emptying in response to eating hard-boiled eggs, it was shown, that in some patients, impaired emptying may be the result of excessive accommodation of the stomach with a delay in the movement of solid foods from the fundal to the antrum [35]. This observation suggests that stimulation of the proximal part of the stomach with reduced gastric accommodation may actually enhance gastric emptying in patients with gastroparesis.

In recent years, it has been increasingly recognized that patients taking opioid medications for a long time may develop gastroparesis [36]. Opioids can cause pyloric dysfunction in addition to inhibiting the motor function of the antrum, which contributes to delayed gastric emptying [37]. Therefore, it is important to assess whether targeted pyloric exposure or inhibition of opioid action may be a therapeutic approach to treat delayed gastric emptying due in part to pyloric dysfunction. Although the classical pharmacological approach to the treatment of pyloric dysfunction in gastroparesis includes injections of botulinum toxin (there is experience indicating its effectiveness, especially with injections in higher doses) [38], but the placebo-controlled study [39] did not demonstrate the effectiveness of this method.

In most countries, only two drugs are approved for use in the treatment of gastroparesis: metoclopramide and domperidone. Both drugs are antagonists of dopamine (D_2) receptors. The action of endogenous dopamine trasmitter is to inhibit the release of acetylcholine, which is accompanied by a decrease in motility of the stomach and proximal small intestine [40]. These inhibitory effects of endogenous dopamine are eliminated when D 2 antagonists are prescribed. -Receptors. Overall, metoclopramide and domperidone have shown similar efficacy in relieving symptoms, although side effects from the central nervous system have been more commonly observed with metoclopramide [41].

It is important that domperidone has an antiemetic effect. The recommended initial dose of domperidone for gastroparesis is 10 mg intravenously and can be increased (if necessary) to 20 mg intravenously at bedtime. In a recent study in Japan, the use of domperidone was found to be safe in the first trimester of pregnancy, without causing an increased risk of common serious congenital malformations in the fetus [42]. The safety of domperidone in relation to the

development of severe ventricular arrhythmias was confirmed in a recent study [43], in which the use of the drug did not increase the risk of developing rhythm disturbances and was as safe as the use of itopride and mosapride (not registered in the Russian Federation). A systematic review of 28 studies showed a 64% reduction in symptoms, a 67% reduction in hospitalizations, and an acceleration in gastric emptying in 60% of patients with diabetic gastroparesis, with the risk of central nervous system side effects being much lower than with metoclopramide because domperidone does not cross the blood-brain barrier [44]. The safe use of domperidone as a drug that stops vomiting was described in 1977 in 27 patients with developed postoperative nausea and vomiting [45]. In clinical practice, the recommended dose of domperidone is from 10 mg 3 r / day and before bedtime (last dose) [44]. It is recommended to avoid its use only in those patients whose adjusted$_{QT\,c}$ interval on the electrocardiogram is >470 ms for men and >450 ms for women [46].

In the study, it was shown that nocturnal duodenogastric reflux of bile and pH of the stomach in patients with functional dyspepsia decreased significantly after treatment with domperidone ($p = 0.015$, $p = 0.021$) [47]. The severity of nocturnal dyspeptic symptoms was also significantly reduced after treatment with domperidone ($p=0.010$, $p=0.015$, $p=0.026$), which was positively correlated with a decrease in nocturnal bile reflux or stomach pH ($r=0.736$, $r=0.784$, $r=0.753$ or $r=0.679$, $r=0.715$, $r=0.697$, $p=0.039$, $p=0.036$, $p=0.037$ or $p=0.043$, $p=0.039$, $p=0.040$) [47]. Therefore, when patients with functional dyspepsia experience nocturnal dyspeptic symptoms that may be associated with excessive nocturnal duodenogastric bile reflux, domperidone therapy may alleviate these symptoms.

A similar positive effect was obtained when domperidone was included in the treatment of patients with chronic superficial gastritis. As the objects of the study, 96 patients with chronic superficial gastritis were selected, which were divided into a control group (n = 48) and a test group (n = 48) using a double-blind method [48]. Patients in the control group received omeprazole, while patients in the test group received domperidone in combination with omeprazole. Clinical effects in both groups were observed and analyzed. After treatment, the improvement in the test group, where domperidone was additionally prescribed, was higher than in the control group ($p<0.05$). The overall response rate in the test group was 97.92% (47/48), which is higher than in the control group (75.00%). After treatment, the effect of gastric mucosal repair in the test group was higher than in the control group ($p<0.05$) [48]. Based on the results obtained, it was concluded that domperidone in combination with omeprazole allows to achieve an ideal effect in the treatment of patients with chronic superficial gastritis, which is of great importance for treatment and prognosis.

At the moment, the use of domperidone (Motilorus®) as an antiemetic remains relevant. In a study conducted in 2019 [49], a survey found that about 45% of italian doctors surveyed prescribed prophylactic antiemetics at the beginning of treatment with opioids. Prokinetics such as metoclopramide and domperidone (84%) were most often prescribed for this purpose, followed by 5-HT_3 antagonists. Receptors (8%), neuroleptics (6%), and corticosteroids (2%). In a study [50] to assess the safety of domperidone in the treatment of nausea and vomiting associated with dihydroergotamine infusion in patients with migraine, 103 consecutive hospitalizations of 90 patients admitted for intravenous dihydroergotamine were analyzed. Most patients were referred to the treatment of chronic migraine with aura (n = 53), the rest - to the treatment of

migraine without aura (n = 46). Domperidone was administered in 85 out of 103 cases and was well tolerated in doses up to 80 mg / day. A significant side effect in the form of akathisia was observed in only one patient. The initial QT-corrected ECG (QT_c) was obtained in all patients. Repeated ECG after domperidone was performed in 21 patients, the initial characteristics of which did not differ from the group as a whole. The QT_c interval did not differ before and after the administration of domperidone. Thus, domperidone was found to be safe in the treatment of nausea associated with the infusion of dihydroergotamine in the hospital.

Recent recommendations for the management of patients with functional dyspepsia based on evidence-based medicine recommend the use of prokinetic drugs as second-line therapy, in particular dopamine receptor antagonists (evidence level B) and 5-$HT_{4\text{-receptor}}$ agonists (level of evidence B) [51]. As for updated recommendations for the diagnosis and treatment of refractory gastroesophageal reflux disease (GERD), the addition of Prokinetics in the treatment regimen of patients did not allow to achieve better control over the symptoms of the disease, but contributed to an improvement in quality of life indicators [52]. A recent meta-analysis [53] of publications including randomized controlled trials comparing the combined use of proton pump inhibitors (PPIs) plus a prokinetic with PPI monotherapy for overall improvement in GERD symptoms analyzed 16 studies involving 1446 patients (719 in the PPI plus prokinetic group and 727 in the PPI monotherapy group). The results of this study showed that treating patients with GERD with PPIs plus prokinetics led to a significant reduction in GERD symptoms regardless of the type of prokinetic, refractory and ethnicity of the patients. In addition, it was found that treating patients with PPIs plus prokinetics for at least 4 weeks was more effective than PPI monotherapy in terms of overall symptom improvement. however, the adverse events observed in response to treatment with a combination of PPIs plus prokinetics did not differ from those observed with PPI monotherapy [53, 54].

CONCLUSION

Extensive research has now been conducted on the effects of different classes of drugs with prokinetic effects, targeting various pathophysiological mechanisms, including impaired antroduodenal coordination, manifested by subjective symptoms and objective delay in gastric emptying. The results obtained open up good prospects for the development of effective methods of treating functional dyspepsia and gastroparesis. The drug domperidone used today in clinical practice (for example, the drug Motilorus®) is still relevant: in the treatment of patients with functional dyspepsia, gastroparesis and GERD, it is recommended to take it in combination with PPIs.

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