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THE PRACTICE OF DOMPERIDONE IN PATIENTS WITH GASTRIC AND INTESTINAL DYSPEPSIA.

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Abstract:

Prokinetic drugs (prokinetics) are drugs that increase and coordinate muscle contractions of the gastrointestinal tract (GI tract), including coordination between different segments of the intestine, thereby enhancing the movement of intraluminal contents. Contemporary approaches to the use of prokinetics in the treatment of motor disorders of the gastrointestinal tract are considered in the overview. The results of studies of various classes of drugs with a prokinetic effect and aimed at various pathophysiological mechanisms, including a violation of antroduodenal coordination, manifested by subjective symptoms and objective delay in gastric emptying, are presented. The drug Domperidone, currently used in clinical practice and registered in Uzbekistan, 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, possesses a positive safety profil when used according to registered indications.

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

INTRODUCTION

Prokinetic medication (prokinetics) are drugs that strengthen and coordinate the muscular contractions of the gastrointestinal tract (GI tract), including coordination between different segments of the intestine, thereby increasing the movement of intraluminal contents [1]. Prokinetics demonstrate pharmacological activity in 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 various 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, while pain is not a typical symptom of delayed gastric emptying [2]. Disorders of gastric accommodation 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 delayed stomach emptying, about 25% have impaired gastric accommodation, and about 25% have a combination of these motor dysfunctions [3].

The identification of stomach emptying disorders requires an accurate test. Currently, there are three direct and one indirect measurement of stomach accommodation. The 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 a pliable polyethylene balloon 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], intraluminal manometry with easy access in the proximal part of the stomach [5]. Indirect measurement of gastric accommodation occurs by taking a nutritious drink at a constant rate of its intake until the maximum permissible is reached, this method allows you to assess the feeling in the stomach [6]. The use of this method also allows you to indirectly assess the accommodation of the stomach, if the caloric content of the drink is less than 750 cal., as there is a linear correlation between the use of this method and the volume of gastric accommodation measured by the barostat, with the caloric content of liquid nutrition below 750 cal. [6]. There had been made attempts for using two-dimensional visualization of the proximal stomach region immediately after eating in order to estimate the stomach accommodation, however it was later found that these measurements were inaccurate compared to the three-dimensional image, and therefore the 2D visualization method requires further validation [7]. The relationship between the acceleration of stomach emptying and the improvement of symptoms against the background of domperidone

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use has been demonstrated [2]. Gastric emptying disorders can be reduced by acting on specific receptors, including serotonergic 5-HT4, as well as dopamine D2/3 receptors and neurokinin 1 receptors (NK1) [8]. In fact, approaches to the improvement of postprandial accommodation were associated with a decrease in the symptoms of functional dyspepsia, for example, with use of the serotonergic agonist 5-HT1A buspirone, or using acothiamide, an acetylcholinesterase antagonist and an antagonist of presynaptic M1 and M2 muscarinic receptors [8]. These muscarinic receptors are involved in inhibiting the release of acetylcholine. Consequently, being an antagonist of these receptors and inhibiting acetylcholinesterase, acotiamide leads to an increase in the local level of acetylcholine, which is a stimulating transmitter in the intestinal nervous system and parasympathetic nervous pathways [9].

Disorders of the pylorus' function are difficult to assess noninvasively, and two approaches are currently available that require intraluminal measurements. This is anthropiloroduodenal manometry and the use of the Endoflip device (endoscopic functional probe for visualization of the lumen of the stomach). When conducting anthropiloroduodenal manometry, closely located pressure 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].

A few agonosts of "new generation" 5-HT4 receptors are selective for 5-HT4 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 U.S. Food and Drug Administration (FDA) for the treatment of chronic constipation. A randomized placebo-controlled cross—sectional study involved 34 patients with motor disorders of the upper gastrointestinal tract (28 with idiopathic, 6 with diabetic gastroparesis), some of them received prucalopride 2 mg 1 r / day, some - placebo for 4 weeks. with a 2-week washing period. Prucalopride was effective in relieving symptoms caused by general gastroparesis according to the index of cardinal symptoms of the subscale of nausea/vomiting, satiety/fulness and bloating, while also improving the overall assessment of the quality of life of patients [13]. Similarly, the effectiveness of velusetrag has been shown in the treatment of patients with diabetic and idiopathic gastroparesis [14]. Intravenous administration of felcisetrag was accompanied by a significant acceleration of gastric emptying, transit through the small intestine and colon emptying compared with the use of placebo in patients with gastroparesis and previously confirmed delay in gastric emptying; at the same time, the drug was well accepted [15]. In a randomized study [16] in two parallel groups, the drug felcisetrag (TAK-954), administered to patients on artificial ventilation and with intolerance to enteral nutrition, defined as a residual stomach volume of ≥200 ml, led to an increase in the proportion of patients with normal gastric emptying compared with metoclopramide, prescribed at 10 mg 4 p /day. Velusetrag and felcisetrag (TAK-954) did not significantly affect the tone of coronary vessels according to pharmacological studies. In addition, these drugs did not have a negative effect on the heart rate and platelet function [17]. Felcisetrag has a high affinity (pci 9.4) for human recombinant 5-HT4 receptors with more than 2000-fold selectivity towards these receptors [18].

Another potential mechanism for enhancing the neuromuscular function of the stomach is an anti-inflammatory effect, which may contribute to the stimulation of the vagus nerve. This was demonstrated using the 5-HT4 agonist prucalopride, which modified the reaction of T2 helper cells and reduced the intensity of postoperative intestinal obstruction [19].

In case of the disorders in the upper gastrointestinal tract associated with hypersensitivity of the stomach, such as functional dyspepsia, the dopaminergic antagonist D2/3 trazpiroben (TAK-506) (there is no a registration in the Russian Federation) was taken as a nutritious drink for 1 week, which led to a significant expansion in the volume of the stomach compared to the initial level [20]. Morover in case of the disorders in a placebo-controlled study [21], the administration of the NK1 receptor antagonist aprepitant was accompanied by an improvement in the clinical symptoms of gastroparesis, including nausea. The given effect may reflect the well-known influence of NK1 receptor antagonists on the emetic center in the brain stem, similar to the action related to the reduction of chemotherapy-induced vomiting. Another potential mechanism of the symptomatic effect may be related to an increase in the volume of the stomach on an empty stomach and accommodation without a negative effect on stomach emptying, which was demonstrated in a study involving healthy volunteers [22]. According to the results of a randomized controlled trial [23], the use of a new NK1 receptor antagonist — tradipitant (not registered in Uzbekistan) was accompanied by an improvement in the symptoms of gastroparesis for 4 weeks.

Another promising direction for improving gastric motor skills is the use of ghrelin-receptor agonists. Ghrelin consists of 28 amino acids, it is mainly localized in the stomach, stimulates appetite. The introduction of a pharmacological dose of recombinant human ghrelin increased the tone of the proximal

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stomach due to central and peripheral effects [24], and in some studies it also accelerated stomach emptying in patients with gastroparesis [25]. Synthetic pentapeptide, an agonist of the ghrelin receptor (RM131), has 130 times more powerful effects than natural ghrelin [26, 27]. The ghrelin receptor agonist relamorelin increases the frequency of distal antral contractions without interfering with stomach accommodation and without changing the saturation after eating in healthy volunteers, which distinguishes its action from the action of the macrolide antibiotic erythromycin [28].

One of the most studied medications with a prokinetic effect are motilin receptor agonists. They include macrolide antibiotics that stimulate gastrointestinal motilin receptors (especially gastric). 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 attractive aspects of erythromycin is that it stimulates fundal and antral contractions, while simultaneously suppressing the contractile ability of the pylorus [30, 54, https://scholar.google.com/scholar?oi=bibs&cluster=16572586286806347167&btnI=1&hl=ru]. The current recommended dose for hospitalized patients with gastroparesis is 1.5–3.0 mg/ kg (intravenous infusion for 45 minutes) every 6-8 hours, 125 mg orally is recommended for outpatient treatment of gastroparesis for several weeks. Side effects that occur with erythromycin treatment include abdominal pain, nausea and diarrhea. The greatest caution should be exercised when using erythromycin concomitantly with medications that are metabolized with the participation of cytochrome P450 (CYP) 3A4 isoenzyme (for example, diltiazem, verapamil or domperidone), whereas drug interactions can cause sudden cardiac death [31].

One of the promising directions of prokinetic therapy is the influence on the bottom of the stomach. Studies have shown that the use of acotiamide improves 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-HT4 receptor agonists, such as tegacerod (not registered in the Russian Federation), in patients with functional dyspepsia with normal gastric emptying was also accompanied by increased gastric accommodation [34]. This provides the basis for their use in functional dyspepsia. In a study using simultaneous measurement of stomach accommodation and emptying in response to eating hard-boiled eggs, it was shown that in some patients, a disturbance of emptying may be the result of extra gastric accommodation with a delay in the movement of solid food from the fundal to the antrum [35]. This observation suggests that stimulation of the proximal stomach with reduced gastric accommodation may actually enhance stomach 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 emptying of the stomach [37]. Therefore, it is important to assess whether targeting the pylorus or inhibiting the action of opioids may be a therapeutic approach to the treatment of delayed gastric emptying, partly due to pyloric dysfunction. Although the classical pharmacological approach to the treatment of pylorus dysfunction in gastroparesis includes injections of botulinum toxin (there is experience indicating its effectiveness, especially when injected at higher doses) [38], a placebo-controlled study [39] did not demonstrate the effectiveness of this method.

In most countries, only two drugs are approved for use for the treatment of gastroparesis: metoclopramide and domperidone. Both drugs are antagonists of dopamine (D2) receptors. The effect of the endogenous dopamine transmitter is to inhibit the release of acetylcholine, which is accompanied by a decrease in the motility of the stomach and the proximal small intestine [40]. These inhibitory effects of endogenous dopamine are eliminated when D2 receptor antagonists are prescribed. In general, metoclopramide and domperidone showed similar efficacy in relieving symptoms, although side effects from the central nervous system were more often observed when using 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 before bedtime. In a recent study conducted in Japan, the use of domperidone proved to be safe in the first trimester of pregnancy, without causing an increased risk of general 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 itoprid and mosaprid (not registered in the Russian Federation). A systematic review of 28 studies showed a decrease in symptoms in 64%, a decrease in hospitalization in 67% and an acceleration of gastric emptying in 60% of patients with diabetic gastroparesis, while the risk of side effects from the central nervous system was much lower than with metoclopramide, since domperidone does not penetrate the blood-brain barrier [44]. The safe use of domperidone as an anti-

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vomiting drug was described as early as 1977 in 27 patients with postoperative nausea and vomiting [45]. In clinical practice, the recommended dose of domperidone is from 10 mg 3 r / day and before bedtime (last intake) [44]. It is recommended to avoid its use only for those patients whose adjusted QTc interval on an electrocardiogram is >470 ms for men and >450 ms for women [46].

The study showed that nocturnal duodenogastric bile reflux and gastric pH in patients with functional dyspepsia significantly decreased after treatment with domperidone (p=0.015, p=0.021) [47]. The severity of nocturnal dyspeptic symptoms was also significantly reduced after domperidone treatment (p=0.010, p=0.015, p=0.026), which positively correlated with a decrease in nocturnal bile reflux or gastric 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, if nocturnal dyspeptic symptoms occur in patients with functional dyspepsia, which may be associated with excessive nocturnal duodenogastric bile reflux, domperidone therapy can alleviate these symptoms.

A similar positive effect was obtained when domperidone was included in the therapy of patients with chronic superficial gastritis. 96 patients with chronic superficial gastritis were selected as subjects of the study, who 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 were observed and analyzed in both groups. After treatment, the improvement of indicators 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 restoring the gastric mucosa 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 can achieve an ideal effect in the treatment of patients with chronic superficial gastritis, which has a great significance for treatment and forecast.

At the moment, the use of domperidone (Motilium ®) as an antiemetic remains relevant. In a survey conducted in 2019 [49], it turned out that about 45% of the surveyed Italian doctors prescribed preventive antiemetics at the beginning of opioid treatment. Prokinetics such as metoclopramide and domperidone were most often prescribed for this purpose (84%), followed by 5-HT3 receptor antagonists (8%), neuroleptics (6%) and corticosteroids (2%). In the research held [50] to evaluate the safety of domperidone in the treatment of nausea and vomiting related to dihydroergotamine infusion in patients with migraine, 103 consecutive hospitalizations of 90 patients admitted for intravenous administration of dihydroergotamine were analyzed. Most of the patients were referred for the treatment of chronic migraine with aura (n=53), the rest — for the treatment of migraine without aura (n=46). Domperidone was administered in 85 out of 103 cases and was accepted at doses up to 80 mg/day. A significant side effect in the form of akathisia was observed in only one patient. An initial ECG with an adjusted QT interval (QTc) was obtained in all patients. Repeated ECG after domperidone was performed in 21 patients whose initial characteristics did not differ from the group as a whole. The QTc interval did not differ before and after domperidone administration. Thus, domperidone proved to be safe in the treatment of nausea related to dihydroergotamine infusion in a hospital.

Recently published recommendations on 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-HT4 receptor agonists (evidence level B) [51]. As for the updated recommendations for the diagnosis and treatment of refractory gastroesophageal reflux disease (GERD), the addition of prokinetics to the treatment regimen of patients did not allow for better control of the symptoms of the disease, but contributed to the improvement of quality of life indicators. [52]. In a recent meta-analysis [53] of publications including randomized controlled trials comparing the combined use of proton pump inhibitors (PPI) plus prokinetic with PPIs monotherapy for overall improvement of GERD symptoms, 16 studies involving 1,446 patients (719 in the PPI plus prokinetic group and 727 in the PPI monotherapy group) were analyzed. According to the results of this study, it was shown that the treatment of patients with GERD using PPI plus prokinetic resulted in a significant reduction in GERD symptoms regardless of the type of prokinetic, refractoriness and ethnicity of patients. In addition, it was found that the treatment of patients with the use of PPI plus prokinetic for at least 4 weeks. it was more effective in comparison with PPI monotherapy in relation to the overall improvement of symptoms, while the adverse events observed in response to treatment with a combination of PPI plus prokinetic did not differ from those observed with PPI monotherapy [53, 54].

CONCLUSION

At the moment, extensive researches have been provided to study the effects of various classes of medications with a prokinetic effect, aimed at various pathophysiological mechanisms, including a violation of antroduodenal coordination, manifested by subjective

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symptoms and objective delay in stomach emptying. The obtained results open good prospects for the development of effective methods for the treatment of functional dyspepsia and gastroparesis. Domperidone, a drug currently used in clinical practice (for example, Motilorus ®), is still relevant: in the treatment of patients with functional dyspepsia, gastroparesis and GERD, its use in combination with PPI is recommended.

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