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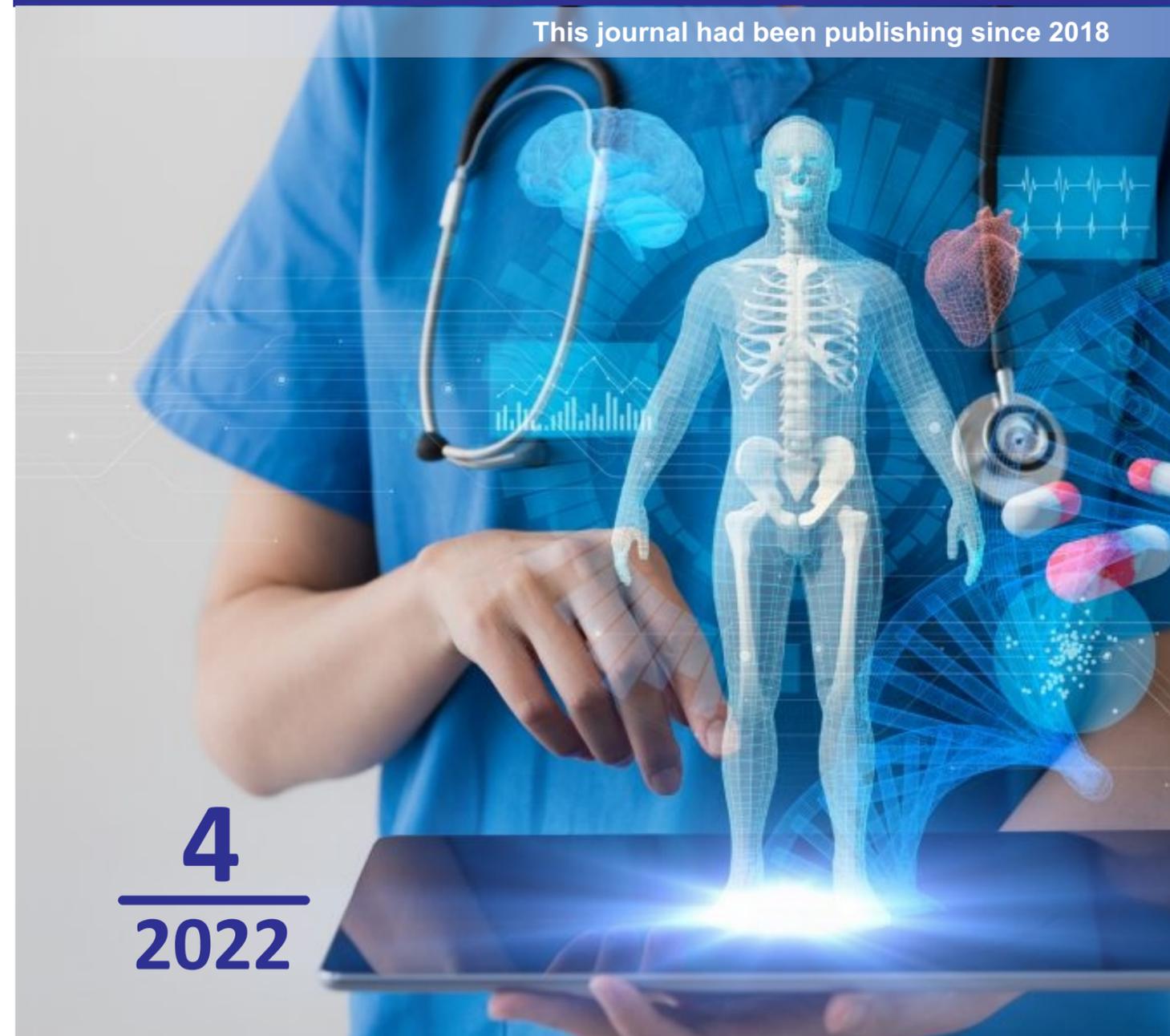


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OPTIMIZATION OF THERAPY FOR GASTROESOPHAGEAL REFLUX DISEASE IN COMORBIDITY WITH FUNCTIONAL DYSPEPSIA

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ABSTRACT

It has been shown that in patients with GERD and functional dyspepsia, the use of proton pump inhibitors leads to a decrease in heartburn and pain behind the sternum. However, symptoms such as regurgitation, belching, feeling of early satiety and heaviness after eating were stopped ineffectively. The inclusion in the treatment complex of the prokinetic domperidone at a dose of 10 mg 3 times a day contributed to a more effective regression of symptoms of impaired motility of the esophagus and stomach.

Key words: gastroesophageal reflux disease, functional dyspepsia, proton pump inhibitors, prokinetics.

INTRODUCTION

According to current concepts, gastroesophageal reflux disease (GERD) is a chronic relapsing disease characterized by the development of inflammatory changes in the mucosa of the distal esophagus and/or characteristic clinical symptoms associated with repeated reflux of gastric and/or duodenal contents into

the esophagus. In most patients, the symptoms of GERD are intermittent and the disease itself proceeds in a relatively mild form, which, however, does not mean that these symptoms do not require correction. When managing patients with this disease, it should be remembered that it has the potential to lead to serious complications. Constantly recurring irritation of the lower esophagus can cause the development of esophageal stricture, erosive esophagitis, esophageal cancer, Barrett's syndrome. The latter complication, according to the literature, occurs in <1% of the population, but in the population of patients with long-term GERD, its prevalence is 5-15%. This indicates the importance of timely diagnosis and treatment of patients with GERD [1]. The main direction of treatment in patients with GERD is the suppression of the production of hydrochloric acid, i.e. use of antisecretory therapy, the gold standard of which, according to the Genval Consensus, are proton pump inhibitors. Since the relief of disease symptoms is directly correlated with the duration and rate of blockage of gastric secretion, effective control of gastric pH is one of the main elements of the long-term elimination of GERD manifestations, including esophageal and extraesophageal symptoms and tissue damage.

Approximately 32-60% of patients with GERD have clinical symptoms of functional gastric dyspepsia (FD) syndrome. This cohort of patients with GERD respond poorly to therapy with proton pump inhibitors (PPIs). It is believed that this is due to impaired motility of the esophagus and stomach, which is a pathogenetic rationale for the use of prokinetics in the treatment of comorbid pathology of the esophagus and stomach [2].

PPIs are drugs that inhibit the activity of the enzyme $H^+, K^+ ATPase$, located on the apical membrane of the parietal cell and performing the last step in the synthesis of hydrochloric acid. To date, PPIs are considered the most effective and safe drugs for the treatment of GERD. In clinical trials, they consistently demonstrate the greatest efficacy in the treatment of erosive esophagitis and the relief of GERD-associated symptoms. But even against this background, more than half of patients with GERD are not satisfied with the results of treatment, and 36% need to take additional drugs to control the symptoms of the disease [3].

G.N, J Tytgat, a researcher of acid-related diseases, noted back in 2003 that 20 years of experience with the use of acid secretion inhibitors in the stomach did not lead to the disappearance of cylindrical metaplasia of the esophageal epithelium. This point of view is shared by T. Frieling, who points to the recurrence of GERD in 90% of patients after PPI discontinuation [7]. According to R. Carlsson et al., without maintenance therapy, the recurrence of clinical symptoms of erosive esophagitis is observed in almost 92% of cases.

One of the reasons for the ineffectiveness of GERD therapy is insufficient acid suppression of PPIs. The level of acid suppression achieved by drugs from the PPI group was evaluated in a study by Y. Yuan et al. using 24-hour pH-metry, when against the background of 5–8 days of PPI intake at a standard dose by healthy volunteers, periods of a decrease in pH in the stomach <3 were found, their duration was 27.8–44.1% of the day. A dual dosing regimen was also studied (PPIs were taken 2 times a day for 5-8 days): a decrease in pH <4 was observed within 15-36%, <3 - within 5-28% of the measurement time [3].

Another reason for the lack of effectiveness of antisecretory therapy for GERD is the problem of comorbidity. Comorbidity is the coexistence of two or more syndromes or diseases in one patient, pathogenetically interconnected or coinciding in time. One example of a comorbid pathology of the digestive tract is the combination of GERD and functional dyspepsia (FD). According to systematic reviews, the combined course of GERD occurs in 32-62% of patients with FD. [4] Combined functional pathology of the gastrointestinal tract (GIT) changes the clinical picture of GERD, which complicates differential diagnosis, leads to inadequate prescribing of drug therapy and its low efficiency. All this negatively affects the quality of life of patients [5].

Pharmacotherapy for GERD, in addition to PPIs, also includes prokinetics. The appointment of prokinetics is justified by increasing antropyloric motility, which leads to an increase in the tone of the lower esophageal clearance and a more accelerated evacuation of gastric contents. All of the above effects make it possible to call prokinetics the means of pathogenetic therapy. To date, domperidone (10 mg 3 times a day), itopride (50 mg 3 times a day) are used as prokinetics for GERD. Metoclopramide is used infrequently due to a wide range of side effects.

PURPOSE OF THE STUDY

Compare the clinical efficacy of PPI- lansoprazole and its combination with domperidone in the comorbid course of GERD and FD.

MATERIAL AND RESEARCH METHODS.

For the study, 60 patients with GERD occurring against the background of FD (37 men and 23 women) were selected. The average age was 44 years. The diagnosis was confirmed by EGDFS data and pH-metry with an AGM-03 acidogastrometer (Russia, Istok system). The predominant form was non- erosive reflux disease (71%), in the structure of which 80% of patients had catarrhal esophagitis, in the rest, reflux disease did not have endoscopic manifestations and was detected only on the basis of complaints and pH- metry. In patients with FD, it proceeded in the form of pain symptoms in 25%, in the form of postprandial

distress syndrome in 34%, and in the form of a combination of both symptoms in 41 patients.

All patients were divided into two representative groups. The first group of patients took PPI - lansoprazole (Lantorol[®],) at a dose of 30 mg per day for 4 weeks. The second group of patients was prescribed lansoprazole in a similar dose and domperidone (Peridon[®],) at a dose of 10 mg, 1 tablet 3 times a day before meals for 2 weeks.

Control during treatment was carried out according to a single program, which included a general clinical examination, intraesophageal pH-metry, EGDFS. Reflux-associated symptoms were assessed using the Likert scale. EGDFS, pH-metry and the study of the symptoms of the disease were carried out before the start of treatment and 4 weeks after the completion of the course of treatment.

RESULTS AND DISCUSSION.

Study of the dynamics of clinical manifestations of GERD in the examined patients according to the Likert scale (Table 1) showed that the main characteristic symptoms of the disease in the first place are heartburn - 100%. Next come such symptoms as belching - 82.8%, regurgitation - 53.2% and retrosternal pain - 43.6%. Against the background of the therapy in both groups of patients, the following changes were noted on the Likert scale. In the first group, there was a decrease in symptoms of heartburn by 60.4%, belching by 33.2%, regurgitation by 23.4%. In the second group, the indicators were respectively - 86.0%; 65.5%; 51.0%.

Conducted endoscopic studies showed that in 67.5% of patients of the first group, GERD proceeded in the form of catarrhal esophagitis, and in the remaining 32.5% of patients, erosions were noted in the mucous membrane. In the second group of patients, catarrhal esophagitis was detected in 70% and erosive in 30% of cases. Repeat endoscopy was performed 4 weeks later. After the therapy, the endoscopic picture looked as follows. In the first group of patients, catarrhal esophagitis was observed in 18%, and erosive esophagitis in 17.5% of patients. In the second group, catarrhal esophagitis was verified in 10.5%, and erosive esophagitis - in 8.5% of patients. The study determined in the first group of patients an improvement in the endoscopic picture of GERD by 62.5%, and in the second group by 85%.

Conducted transendoscopic and topographic pH-metry showed that when using lansoprazole, there was a significant increase in the pH level in the zone of active acid formation - the anterior and posterior walls of the body of the stomach. The effectiveness of antisecretory therapy is usually considered effective if during treatment the pH level is within 4.0. When using PPIs, the pH level in the body of

the stomach by the 4th week was within 3.8. In the second group of patients who took lansoprazole in combination with domperidone already in the 4th week, the pH level in the zone of active acid formation was at the level of 4.6. The pH level in the acid neutralization zone, which is located in the antalar section of the stomach, when using lansoprazole, was at the level of 3.9 (at a rate of 4.6). In the group of patients taking combination therapy, on the 4th week, the pH level in the antrum was at the level of normal values - 4, 3.

As a result of the study, clinical efficacy and good tolerability of the treatment were noted, no cases of drug withdrawal or side effects were observed.

Thus, in general, there is a high efficacy of lansoprazole. (Lantrol[®]) in relation to the relief of clinical symptoms and healing of catarrhal-erosive lesions of the esophagus. When using the drug, pain and heartburn stop in most patients in the first days of treatment, and the healing of erosive esophagitis, depending on the initial severity, in patients within 4 weeks. Lansoprazole is highly effective in the treatment of GERD. However, when a patient with GERD has a comorbidity with FD symptoms, the relief of symptoms such as belching, nausea, and regurgitation occurs to a much lesser extent, since these symptoms are more associated with upper GI dysmotility. In this case, combining a PPI with a prokinetic, in this case domperidone (Peridon[®]) has a more pronounced clinical effect. The advantage of domperidone is that the drug does not pass through the blood-brain barrier, due to which it is practically devoid of side effects (no extrapyramidal effects) characteristic of metoclopramide. Inclusion in complex therapy of domperidone allows you to restore the propulsive motor activity of the esophagus, stomach, duodenum. The obtained results indicate that with the help of domperidone it is possible to successfully control the clinical symptoms of NERD and FD in patients with combined functional pathology, as well as the pH level in the esophagus.

In the gastroenterological literature of recent years, a number of reports have appeared that the use of domperidone can provoke a number of serious cardiovascular disorders, ranging from prolongation of the QT interval to the occurrence of arrhythmias of the "pirouette" type [6]. A retrospective analysis of patients with nausea and vomiting who received domperidone from 2009 to 2013, according to Investigational's new drug study protocol New Drug (IND) showed the following results [7]. Doses of the drug ranged from 40 to 120 mg/day, with 90% of patients receiving a dosage of 80 to 120 mg instead of the recommended dose of 40 mg (doses for nausea and vomiting were revised upwards from 30 to 40 mg). It should be noted that in 73% of patients treated with domperidone, there was a decrease in nausea and vomiting. ECG showed a mean QTc at baseline of

424 milliseconds (ms) \pm 28.4 (SD) compared to 435 ms \pm 27.2 (SD) at follow-up (non-significant increase). In 10 of these patients, QTc prolongation was prolonged in the range from 453 to 509 ms without any rhythm disturbances [8].

The question arises: why is the issue of pronounced side effects of the drug now being actively considered, which fundamentally changed the attitude of the medical community towards it? To this end, it is necessary to chronologically consider the entire process of information receipt and evaluation, as well as correctly correlate patient groups and dosages used for treatment. Food and Drug Administration (FDA) June 7, 2004 issued a warning that distribution of any product containing domperidone is illegal. The FDA took this action out of concern about the potential health risks associated with the use of domperidone lactating women to improve breast milk production. Although initial reports of serious adverse events (cardiac arrhythmias, cardiac arrest and sudden death) were associated with intravenous domperidone and high blood concentrations, the possibility that the simultaneous use of moderate or strong inhibitors of CYP3A4 may lead to an increase in the concentration of domperidone and, consequently, to an increased risk of cardiac arrhythmias, cardiac arrest and sudden death [9]. It is logical: the use of the off-label drug, in principle, is never welcome. On the other hand, an attempt to expand the indications for use should always be balanced: the penetration of the drug through milk (and it was used in high doses intravenously, then orally) is always fraught with adverse effects on the infant (especially without taking into account the state of the cardiovascular system). However, the FDA recognizes that some patients with severe GI dysmotility (GERD, gastroparesis, and chronic constipation) who find it difficult to manage symptoms with available therapy may be treated with domperidone. According to the medical literature, the standard dose of domperidone is 10 mg 3 or 4 times a day [9]. A balanced approach to prescribing the drug allows not only to achieve a good result, but also to eliminate the risks of side effects. Accordingly, when prescribing domperidone, special care should be taken in patients with risk factors for cardiac arrhythmias (old age, the presence of diseases of the cardiovascular system), exclude the use of macrolide antibiotics and antifungal drugs that increase its concentration in the blood, and prescribe the recommended dosage of the drug. Compliance with the simplest rules will allow not only to avoid negative effects, but also to increase the effectiveness of the therapy.

Table 1**Dynamics of clinical manifestations of GERD in the examined patients**

Symptoms	Number of points on the Likert scale			
	I group (before treatment)	I group (after treatment)	II group (before treatment)	II group (after treatment)
Heartburn	4.5±0.3	1.2±0.2	4.4±0.5	1.5±0.3
Belching	3.2±0.2	1.8±0.3	3.1±0.3	2.0±0.1
regurgitation	2.4±0.5	1.6±0.1	2.4±0.2	1.9±0.3
Retrosternal pain	2.2±0.7	0.7±0.4	2.3±0.5	1.2±0.2

Table 2**Endoscopic characteristics of GERD in examined patients**

	Catarrhal esophagitis		Erosive esophagitis	
	before treatment	after treatment	before treatment	after treatment
I group (n -40)	27 (67.5%)	4 (10.0%)	13 (32.5%)	3 (7.5%)
II group (n -40)	28 (70%)	7 (17.5%)	12 (30.0%)	5 (12.5%)

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