BASAL GASTRIC SECRETION AS A PROGNOSTIC CRITERION OF PROTON PUMP INHIBITORS EFFECTIVENESS

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INHIBITORS EFFECTIVENESS
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Introduction. The development of prognostic criteria for the effectiveness of proton pump inhibitors (PPIs) in the conditions of increasing resistance of Helicobacter pylori to antibiotics is relevant. We studied results of express gastro-pH monitoring (before the start of treatment and on the 5-7th day of PPI administration). We analyzed the results of topographic express pH-metry for 2003-2015 in 157 patients with acid-dependent diseases associated with Helicobacter pylori. Statistical calculations were performed using MedCalc®Software bvba. In the statistical processing of the results, we used the arithmetic mean and its standard, the probability of the difference was determined by the Student’s t-test; Spearman’s rank correlation coefficient was determined; ROC curve analysis was performed. We established a correlation between the level of HCl basal secretion before the treatment start and the effectiveness of the PPIs acid-blocking action for the successful H.p eradication according to the following indicators of topographic express pH-metry: min pH - 0.21, X pH - 0.22, Mo pH - 0.35 and Me pH - 0.37. At the same time, for max pH, such a relationship was absent (p>0.05) and the Spearman rank coefficient was 0.05, respectively express gastro-pH monitoring before the start of PPIs can be used to predict the effective acid-blocking action of PPI. Express-gastro-pH-monitoring can be used as a screening technique for predicting the effectiveness of successful Helicobacter pylori eradication.

Keywords: Helicobacter pylori, acid-dependent diseases, secretion of hydrochloric acid, pH-monitoring.

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Introduction. Nowadays the role of the bacterium Helicobacter pylori (H.p.) as an etiological and pathogenetic factor of the acid-dependent disease of upper gastrointestinal tract is beyond doubt.

At the same time, the growing resistance of H.p. to previously effective regimens of anti-Helicobacter therapy is one of the problems in modern gastroenterology, which prevents the provision of eradication sufficient levels [10, 16].

According to a study by I. Thung et al. (2016) the persistence of H.p. to clarithromycin in countries such as Japan and Italy is more than 30%, in Turkey - more than 40%, and in Sweden and Taiwan, the resistance of H.p. to clarithromycin was detected in less than 15% of examined patients [26]. In the study by L. Bujanda et al. (2021) which was conducted in European countries for the period 2013-2020, about 4,000 biopsy samples taken from infected H.p. patients were determined resistance to the main anti-helicobacter antibiotics: clarithromycin, levofloxacin and metronidazole in 25, 20 and 30% of all examined biopsies, respectively [1].

In 2011, a group of Kyiv scientists established that the resistance of H.p. to drugs from the group of nitroimidazoles was 31.9%, cross-resistance between different generations of nitroimidazoles - 11.6%; to clarithromycin - 10.1%, cross-resistance between clarithromycin and metronidazole derivatives in 5.8% [22].

Pending the emergence of new antibacterial drugs, a reasonable strategy is to select a combination of agents based on an individualized approach based on knowledge of antibiotic susceptibility [8, 11].

The search for ways to optimize anti-Helicobacter therapy is relevant in the context of the choice of approaches to the treatment of diseases of the upper gastrointestinal tract (GIT). In these conditions, attention is drawn to the fact that a significant factor influencing the success of the eradication of H.p. there is sufficient acid-blocking effect of proton pump inhibitors (PPIs).

It is known that the bacterium H.p. is sensitive to antibiotics only during the vegetative phase of replication. The replicative phase begins at neutral acidity, and in a weakly acidic environment acquires a coccoid form that is resistant to antibacterial drugs [9, 13, 19, 23].

Also, inhibition of HCl secretion by 20% reduces its destructive effect on antibiotics, which are used during the eradication treatment of H.p., which leads to an increase in their concentration in the gastric mucosa and blood plasma [2, 21].

Therefore, it is extremely important to increase the pH of the stomach with the help of PPIs, because insufficient acid inhibition can create conditions for the presence of some bacteria in non-replicative forms that are insensitive to antibiotics [9, 18].

According to the current Maastricht V and VI, PPIs are recommended for the treatment of Helicobacter pylori infection in a standard dosage twice a day: omeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg or rabeprazole 20 mg. Low-dose PPIs are not recommended because they are not sufficiently ineffective, as clearly...
established a direct relationship between the success of the eradication of H.p. and acid inhibition. M. Sugimoto et al. (2007) obtained from their results. It was established that patients with successful H.p. eradication, the value of the median 24-hour intragastric pH was probably higher (6.4 (5.0-7.6) units) than in patients with unsuccessful eradication of H.p. (5.2 (2.2-6.2) units) [25].

SYP2C19 gene polymorphism divides the human population into three phenotypic subgroups: rapid metabolizers, intermediate metabolizers, and slow metabolizers. It is believed that 2/3 of the Caucasian population belongs to fast metabolizers and that is why the effectiveness of H.p. eradication in such patients can decreased significantly [12, 14].

According to the results of his own research, J. Bujanda et al. (2021) suggested the possibility of using higher doses of PPIs as an alternative to adding new antibacterial drugs to anti-Helicobacter pylori regimens [1].

Sensitivity H.p. to antibacterial drugs and cytochrome P-450 activity (CYP2C19 genotype) are important in choosing a PPI dose. However, the implementation of these examinations will significantly delay the initiation of anti-Helicobacter treatment and lead to increased costs, especially in countries with low levels of medical support [8, 20].

Given that PPIs are a mandatory component of most H.p. treatment regimens, it is advisable to study the presence of prognostic criteria that could allow the assessment of PPI action to achieve successful H.p. eradication.

In particular, in scientific works, S. G. Melashchenko (1997) noted that the daily intragastric pH in people with duodenal ulcer disease is significantly lower compared to practically healthy people at any time of the day (daily median 1.42 versus 1.69 pH units, p<0.01). At the same time, it was established that the level of secretion of hydrochloric acid in the parietal cells of the stomach does not depend on the sex, age of the patients, phase and duration of the disease, smoking [17].

It should be noted that in his research works V.V Chernobrovy used the method of express research of the secretory function of the stomach, comparing the obtained results with the results of daily gastro-pH monitoring. A clear correlation between these methods was described, allowing the use of express gastro-pH monitoring to assess gastric secretory function before and during PPI use [6, 7].

This approach would make it possible to develop criteria for choosing the dose of acid-blocking drugs at the beginning of treatment to improve the effectiveness of H.p. eradication.

The aim of our study was to establish the parameters of intragastric pH parameters based on the results of express gastro-pH monitoring (before the start and on the 5-7th day of PPI intake), which could be used to predict the success of H.p. eradication in patients with acid-dependent diseases.

**Materials and methods**

The results of express gastro-pH monitoring for 2003-2015 in 157 patients with acid-dependent diseases associated with H.p. were analyzed.

For the primary diagnosis of infection of the mucous membrane of the stomach H.p. in patients, one of the listed methods was used: analysis of the levels of antibodies G and M to H.p. in blood serum (Syneo Medical Laboratory); respiratory 13C-urea test (IRIS, Wagner, Germany); rapid urease test (Urea Helicobacter pylori test, Pliva Lachema, Croatia).

Express gastro-pH monitoring was carried out using the AG-1pH-M Acidogastrograph and the gastroenterological system created by the medical-engineering team under the leadership of prof. V. M. Chernobrovyi [3].

Before conducting the research, calibration of the mobile storage device for pH-metric information and the pH-microprobe was carried out in buffer solutions with pH 1.68 and 6.86, heated to a temperature of 370C.

Express gastro-pH monitoring was performed for patients according to the methodology developed by prof. V. M. Chernobrovyi [3, 4].

A pH microprobe was inserted into each patient through the nose (with the use of local anesthesia with a 10% lidocaine solution) to the place of the transition of the esophagus into the stomach, to a depth of 45 cm. Additional landmarks that were used to determine the place of the transition of the esophagus into the stomach are the height of the patient and the data of upper endoscopy (distance from the incisors to the cardia). After the first pH measurement at a depth of 45 cm, further measurements were taken 1 cm later along the length of the gastric canal (from the cardia to the pylorus). In total, 20 intragastric pH measurements were performed: the first 5 pH measurements in the cardiac part of the stomach, 10 measurements in the body of the stomach, and 5 measurements in the antral part of the stomach [5].

According to the method of express gastro-pH monitoring, registration of intragastric pH along the entire length of the stomach was carried out both during the introduction and withdrawal of the pH microprobe.

In each patient who entered the study, express gastro-pH monitoring was performed twice. The first examination was performed before the appointment of acid-blocking pharmacotherapy; the second examination was on the 5-7th day of PPI reception.

In previous works we have developed criteria for the sufficiency of the acid-blocking effect of PPIs for successful eradication of H.p. (max pH > 6.8 units, for X pH > 5.6 units, for Mo pH > 5.7 units [20].

According to the received data of express gastro-pH monitoring on the 5-7th day of PPI intake, two groups of participants were formed. Group № 1 consisted of 77 patients (43 women and 34 men) with acid-dependent diseases with the presence of H.p., in whom the acid-inhibiting effect of PPIs was sufficient in a standard dose twice a day for the
success of H.p. eradication therapy. The average age of group №1 was 40.1±1.8 years old, height 169.1±1.1 cm, weight 71.7±1.6 kg. Group №2 consisted of 80 patients (38 women and 42 men) with acid-dependent diseases with the presence of H.p., in whom, against the background of PPI treatment in a standard dose twice a day, sufficient acid blocking was not observed for successful anti-Helicobacter therapy. The average age of group №2 was 39.8±1.7 years, height 171±1.0 cm, weight 69.7±1.4 kg.

In order to assess the effect of the basal acidity level of the stomach on PPI effectiveness, we performed a comparative analysis of the results of topographic express pH-metry in both groups. There was no difference between group №1 and group №2 in terms of sex, age, height, and body weight (p>0.05), which allowed us to compare the obtained results with each other.

The results of express gastro-pH monitoring were analyzed, namely the following indicators of stomach pH: maximum pH (max pH), minimum pH (min pH), average arithmetic pH (X pH), pH mode (Mo pH), median pH (Me pH).

According to the statistical processing of the obtained results, formulas were used to calculate the arithmetic mean and the standard error of the arithmetic mean. The calculation of the statistical probability of the difference between two samples of the arithmetic mean and its standard error was performed according to the Student's t-test using the appropriate tables [15].

Correlation between indicators: minimum pH (min pH), maximum pH (max pH), arithmetic mean pH (X pH), mode pH (Mo pH), median pH (Me pH) and eradication of H.p., was studied using the non-parametric Spearman method with determination of the Spearman rank correlation coefficient.

To select the optimal threshold value of the diagnostic method to classify the examined, an analysis of ROC curves (Receiver Operator Characteristic) was performed. Using ROC analysis, the sensitivity and specificity of the diagnostic method were determined, as well as the quality of the model was determined to the possibility of prognostic use of the determined indicators of intragastric pH.

Statistical calculations were performed using the MedCalc®Software bvba computer program.

The conducted research fully meets the ethical standards established by the Vinnytsia National Medical University Bioethics Committee (protocol №7 dated November 1, 2023).

Name of research work (state registration number 0117U005123): "Esophagogastroduodenal peptic (acid-dependent) and Helicobacter pylori-associated diseases with a comorbid course: possibilities of esophago-gastro-impedance-pH monitoring in improving diagnosis, treatment and prevention".

Results. Discussion

During the analysis of the results of express gastro-pH monitoring of persons for acid-dependent diseases associated with H.p. disease, before the start of taking PPIs, certain regularities of the secretory function of the stomach were established, depending on the effectiveness of the acid-blocking action of PPIs.

A comparison of the complex of data of express gastro-pH monitoring in patients of group 1 and group 2 showed that in patients with insufficient for effective eradication of H.p. acid-blocking effect of PPI (group №2) probably had lower (p<0.05; p<0.01) values of intragastric pH (min pH, X pH, Mo pH and Me pH) compared to patients with effective acid-blocking effect of PPI (group №1).

So min pH was (2.1±0.12 vs. 2.6±0.16), X pH (3.0±0.14 vs. 3.5±0.16), Mo pH (2.2±0.15 vs. 3.1±0.17) and Me pH (2.2±0.16 vs. 3.2±0.16). At the same time, there was no difference (p>0.05) between the groups in the value of the maximum pH: 5.2±0.18 versus 5.4±0.19. A correlation was established between the level of basal secretion of hydrochloric acid before treatment and the effectiveness of blocking acid with PPIs for successful H.p. eradication according to the following indicators of topographic express pH-metry: min pH - 0.21, X pH - 0.22, Mo pH - 0.35 and Me pH - 0.37. At the same time, there was no such relationship for max pH (p>0.05), and Spearman's rank coefficient was 0.05, respectively (Table 1).

To assess the ability to use a number of indicators of intragastric pH (min pH, max pH, X pH, Mo pH and Me pH) of express gastro-pH monitoring for diagnostic purposes, the sensitivity and specificity of the indicators were calculated, the quality of the model was determined, in particular, the analysis of the ROC curve for minimum pH indicated the best cut-off point >2.2: sensitivity 49.4% (95% CI: 37.8-61.0), specificity 76.8% (95% CI: 66.2-85.4), AUC 0.62±0.05; p<0.009. According to the classification of ROC curve models, this model has an average quality. For peak pH, the best cutoff point >5.88: sensitivity 46.1 (95% CI: 36.5-59.7), specificity 65.9 (95% CI: 50.8-72.7). AUC 0.53±0.05; p>0.05. According to the classification of ROC curve models, this model has unsatisfactory quality. For X pH, the best cutoff point is >7.48: sensitivity 77.9 (95% CI: 72.9-90.7), specificity 42.7 (95% CI: 28.4-50.4). AUC 0.63±0.04; p<0.004. According to the classification of ROC curve models, this model has an average quality. For pH Mo, the best cutoff is >2.35: sensitivity 61.0 (95% CI: 49.2-72.0), specificity 62.2 (95% CI: 49.6-71.6). AUC 0.72±0.04;
According to the classification of ROC-curve types, the model for Mo pH, as well as the model for Me pH, are of sufficient quality (Fig. 2). Thus, based on the results of the analysis of express gastro-pH monitoring before the start of PPI use, we have established criteria that allow us to predict the effectiveness of the acid-inhibiting effect of PPI, which is necessary for the successful course of H.p. eradication. Based on the obtained results, it was concluded that express gastro-pH monitoring before the use of PPIs can be used to predict the effectiveness of acid blocking with the help of PPIs for successful anti-Helicobacter therapy.

Since it is believed that 2/3 of the Caucasian population belong to fast metabolizers, it is advisable to determine the activity of cytochrome P-450 (CYP2C19 genotype) in order to select the optimal dose of PPI [12, 14, 24]. However, these examinations will significantly delay the start of anti-helicobacter treatment and lead to an increase in costs, and in countries with limited medical support, which includes Ukraine, the determination of cytochrome P-450 activity will be inaccessible to most patients [20].

Guided by literature data, we wanted to conduct a comparative analysis of basal gastric secretion in patients with acid-dependent gastroesophageal diseases depending on the response to PPI intake and to consider indicators of express gastro-pH monitoring as markers for predicting the effectiveness of standard PPI dosing during anti-Helicobacter therapy. The basis for the distribution of patients into groups was the results of control express gastro-pH monitoring, conducted on the 5-7th day of anti-helicobacter treatment.

Conclusions and prospects for further development

1. To ensure the successful eradication of Helicobacter pylori infection in patients with acid-dependent diseases associated with H.p. diseases of the upper parts of the gastrointestinal tract require a sufficient acid-blocking effect of the PPI, which can be predicted by the results of express gastro-pH monitoring before the start of treatment.

2. Indicators of intragastric pH according to the data of express gastro-pH-monitoring before the start of treatment should be: min pH >2.2 units, X pH > 2.48 units, Mo pH >2.35 units and Me pH >2.3 units. Under other conditions, the use of standard PPI doses twice a day will not create a sufficient acid-blocking effect for effective eradication.

Express-gastro-pH-monitoring can be used as a screening for predicting the effectiveness of successful H.p. eradication.

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Підвищення резистентності

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початку лікування та на 5-7-й день прийому ИПП). Проведено аналіз результатів експрес-гастро-рН-моніторингу за 2003-2015 рр. у 157 хворих на кислотозалежні захворювання, асоційовані з Helicobacter pylori. Статистичні розрахунки виконували за допомогою програми MedCalc®Software bvba. При статистичній обробці результатів намі використані середньоарифметична та її стандартна, вірогідність різниці встановлювали за t-критерієм Стьюдента; визначали коефіцієнт рангової кореляції Спірмена; проводили аналіз ROC-кривих. Ми встановили кореляцію між рівнем базальної секреції HCl до початку лікування та ефективністю кислотоблокуючої дії ИПП для успішної ерадикації Helicobacter pylori за такими показниками експрес-гастро рН-моніторингу: min pH - 0,21, X pH - 0,22, Mo pH - 0,35 та Me pH - 0,37. Однак для максимального рН такого зв'язку встановлено не було (p > 0,05), а ранговий коефіцієнт Спірмена становив 0,05, відповідно топографічну експрес-рН-метрію до початку прийому ИПП можна використовувати для прогнозування ефективної кислотоблокуючої дії препарату. Отже, експрес-гастро-рН-моніторинг можна використовувати як скринінговий метод для прогнозування ефективності успішної ерадикації Helicobacter pylori.

Ключові слова: Helicobacter pylori, кислотозалежні захворювання, секреція соляної кислоти, рН-моніторинг.