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# Predictive Value of Individual Gastric Secretion Indices and Their Constellations for Predicting the Response of Gastric Mucosal Parietal Cells to Pentagastrin Stimulation and Famotidine Blocking Effect in Patients with Gastric and Duodenal Ulcers

**Introduction.** Gastric and duodenal ulcer disease (UD) in many countries is one of the most pressing problems of gastroenterology and is in the focus of attention of gastroenterologists, physicians, surgeons, as it has a high proportion among other diseases of the digestive tract, often recurs, causes numerous complications, which leads to disability and long-term disability [19, 21]. This is due to its high prevalence and the predominant onset of the disease in young and middle age (in economically developed countries, it is detected in 5.0-10.0 % of the adult population). According to national healthcare professionals, there are about five million patients with UD in Ukraine, with tens of thousands of new cases registered each year and a growing trend in the number of patients [1].

Given the widespread prevalence, complex and multifaceted etiopathogenesis, and multiple negative social and economic consequences, the problem of optimising the treatment of duodenal UD associated with Helicobacter pylori (Hp) infection is one of the most pressing. An important step in the treatment of UD was the approval of the European concept of Hp eradication, which provides clear treatment recommendations and specific regimens for Hp eradication, formulated in the Maastricht Consensus and taken into account in UD treatment protocols [7, 10]. However, it should be noted that all recommended treatment protocols include acid reducing agents (proton pump inhibitors, $H_2$-histamine receptor blockers) without taking into account information about the state of gastric secretion, which may be achlorhydric or even anacidic in certain cases [20, 36].

Despite numerous clinical trials investigating the efficacy of acid-blocking drugs in large cohorts of patients with various pathologies, an important aspect of their use is the assessment of the effect on a particular patient, as it can vary significantly depending on the individual characteristics of the patient's gastric secretion [9, 25]. Assessment of the effect of an acid-reducing drug through its impact on several gastric juice parameters allows for a much deeper characterisation of its impact on the complex mechanism of gastric secretion. This mechanism includes not only the level of acidity, but also the concentration of pepsin, electrolytes, bicarbonates and mucus. Identification of these relationships (constellations) makes it possible to predict the effectiveness of a particular drug and select its dosage for each patient based on the initial indicators of gastric secretion and response to stimulation. This, in turn, improves treatment outcomes, reduces side effects, and achieves higher efficacy of gastric and duodenal ulcers [1, 9, 25].

In summary, studies to predict the effectiveness of stimulating gastric secretion with pentagastrin and the use of $H_2$-histamine receptor blockers in patients with gastric and duodenal ulcers are an appropriate and relevant task that can help improve the effectiveness of treatment, reduce the risk of comorbidities, and increase knowledge about the prescription of acid-reducing drugs in patients with UD [28, 37, 39].

**The aim of the study.** To find out the prognostic value of gastric secretion indices (amount of gastric juice, free hydrochloric acid, total acidity, hydrogen ion rate, pepsin, pepsin rate, potassium ions in gastric juice, N-acetylneuraminic acid in juice, sodium ions in the juice) and their constellations to predict the response of gastric mucosal parietal cells to submaximal stimulation with pentagastrin

and blocking effect of famotidine in patients with gastric and duodenal ulcers.

**Materials and methods.** After obtaining the written consent from patients for the examination following the principles of the Helsinki Declaration of Human Rights, the Council of Europe Convention on Human Rights and Biomedicine, as well as following the legislation of Ukraine, the study was conducted in a randomized manner with preliminary stratification by the presence of an endoscopically confirmed diagnosis of UD in the acute phase (Order of the Ministry of Health of Ukraine N 613 dated September 03, 2014) in 40 patients (28 women (70.0 %) and 12 men (30.0 %) aged 18-68 years) at the 5th City Hospital in Lviv. All patients who participated in the study had a positive urease test for Helicobacter pylori.

To assess the changes in gastric secretion under the influence of submaximal stimulation with pentagastrin and subsequent administration of the $H_2$-blocker of histamine receptors famotidine, a modified version of the fractional sensing technique was used [4, 6, 41]. The technique involved aspiration of the gastric contents on an empty stomach, after which the basal secretion was suctioned every 15 minutes during the first hour. At the beginning of the second hour, patients were injected with a submaximal dose of pentagastrin subcutaneously at the rate of 0.008 mg/kg body weight, after which the secretion was collected every 15 minutes for an hour. At the beginning of the third hour, 40.0 mg of the $H_2$-histamine receptor blocker famotidine (KRKA, Slovenia) was administered intragastrically, after which secretions were collected every 15 minutes for an hour [24].

The following parameters were determined in all portions of gastric juice: the amount of gastric juice, free and total hydrochloric acid (HCl), hydrogen ion ($H^+$) activity and its flow rate, pepsin content and its flow rate (debit), potassium ions ($K^+$) in juice, N-acetylneuraminic acid (NANA) in juice, sodium ions ($Na^+$) in juice. The amount of gastric juice was measured in ml; free and total HCl of gastric juice was determined by the titration method in mmol/l; to assess $H^+$ activity, titration was performed using a pH meter, their flow rate was measured in mmol/h [2, 3, 5]; pepsin content was measured by the colourimetric method in mmol/l [11, 13, 15, 26, 27, 30, 35, 40, 42], its flow rate was measured in mg/h; Potassium ions ($K^+$) in juice were determined by the half-beam photometric method in mmol/l [18]; NANA, as a marker of mucoid secretion, was determined by the resorcinol method in μM/l [8, 12, 14, 22, 23, 31, 32, 34]; $Na^+$ concentration, as a marker of hydrocarbonate secretion, was determined by the half beam photometric method in mmol/l [5, 18].

The study was conducted in three stages. At the first stage, nine indicators of gastric secretion were studied in 40 patients: the amount of gastric juice, free and total HCl, $H^+$ activity and its flow rate, pepsin content and its flow rate, $K^+$ ions in juice, NANA in juice, $Na^+$ ions in juice. A correlation analysis was performed to identify the relationship between the $H^+$ flow rate and the values of other indicators of basal gastric secretion, for which the Pearson correlation coefficients and their corresponding *p*-values were calculated [16, 29].

At the second stage of the study, the response of the parietal gastric glands to submaximal pentagastrin stimulation was assessed, for which all patients were stratified according to the $H^+$ flow rate in gastric juice after stimulation into three groups: hyperacidic, normal (reference values) and hypoacidic.

The nine basal gastric secretion indices mentioned above were also stratified into three subgroups: with elevated (increased), normal and decreased (decreased) values relative to the reference values.

The $\chi^2$-test was used to assess the relationship between baseline values and $H^+$ efflux after stimulation. The results were considered significant at a *p*-value of less than 0.05. To determine the optimal constellations of basal secretion parameters for predicting the response to submaximal pentagastrin stimulation, an optimization task was used to minimize the *p*-value of the z-test by comparing the proportions of individuals who fell into the corresponding constellations [17, 33].

At the third stage, the reaction of the parietal gastric glands to the administration of the $H_2$-histamine receptor blocker famotidine was assessed, stratified according to the $H^+$ flow rate in gastric juice after stimulation into three groups: patients with hyperacidity, normal values (reference values) and hypoacidity. All the studied basal gastric secretion parameters were also stratified into three subgroups: with increased, normal and decreased values relative to the reference values. At this stage, a t-test was performed to compare the mean values of $H^+$ efflux after famotidine administration for each of the nine groups of patients and the mean value of $H^+$ efflux in the entire study sample.

To determine the optimal constellations of basal secretion parameters for predicting the response of the parietal gastric glands to the administration of the $H_2$-histamine receptor blocker famotidine, an optimization task was used to minimize the *p*-value of the t-test by comparing the mean values of $H^+$ debitage in patients who fell into the corresponding constellations with the mean value of $H^+$ debitage in the entire study sample [17, 29].

**Results and discussion.** At the first stage of the study, a correlation analysis was performed to identify the relationship between the hydrogen ion flow rate and the values of other indicators of basal gastric secretion (Table 1).

*Table 1*

**The results of the correlation analysis to identify the relationship between the hydrogen ion flow rate and the values of other indicators of basal gastric secretion (parameters; r; *p*)**

| Parameter | Correlation coefficient r | *p* |
|---|---|---|
| 1 | 2 | 3 |
| The amount of gastric juice | 0.44 | <0.01* |
| Free HCl | 0.85 | <0.01* |

*Contin of the Table 1*

| 1 | 2 | 3 |
|---|---|---|
| Total acidity | 0.87 | <0.01* |
| Pepsin | 0.44 | <0.01* |
| Pepsin flow rate | 0.25 | 0.03* |
| $K^+$ ions in juice | -0.04 | 0.69 |
| NANA in juice | -0.16 | 0.15 |
| $Na^+$ ions in juice | -0.07 | 0.54 |

**Note.** * - the relationship is statistically significant.

Statistical analysis of the results revealed that the $H^+$ flow rate in basal secretion correlates significantly with total acidity (r = 0.87, $p < 0.01$), free HCl (r = 0.85, $p < 0.01$), pepsin flow rate (r = 0.51, $p < 0.01$), juice quantity (r = 0.44, $p < 0.01$), pepsin content (r = 0.25, $p = 0.03$). At the same time, there were no significant relationships between the $H^+$ flow rate in basal secretion and the content of $K^+$, NANA, and $Na^+$ ions in juice.

The values of indicators after submaximal stimulation with pentagastrin are shown in Table 2.

*Table 2*

**Results of the $\chi^2$-test to assess the relationship between basal secretion and hydrogen ion flow after stimulation (parameters; number of people in the group with hyperacidity; normacidity; hypoacidity; n; *p*)**

| Parameter | Group by the content of the parameter | Patients with hyperacidity, n | Patients with normal acidity, n | Patients with hypoacidity, n | *p* |
|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 |
| Amount of gastric juice, ml | increased | 0 | 0 | 0 | 0.37 |
| | normal | 25 | 0 | 1 | |
| | reduced | 47 | 3 | 4 | |
| Free HCl, mmol/l | increased | 2 | 0 | 0 | 0.76 |
| | normal | 12 | 0 | 0 | |
| | reduced | 58 | 3 | 5 | |
| Total acidity, mmol/l | increased | 2 | 0 | 0 | 0.81 |
| | normal | 10 | 0 | 0 | |
| | reduced | 60 | 3 | 5 | |
| $H^+$ flow rate, mmol/h | increased | 42 | 2 | 2 | 0.74 |
| | normal | 12 | 1 | 1 | |
| | reduced | 18 | 0 | 2 | |
| Pepsin, mmol/l | increased | 21 | 1 | 0 | 0.33 |
| | normal | 28 | 0 | 2 | |
| | reduced | 23 | 2 | 3 | |

*Contin of the Table 2*

| 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|
| Pepsin flow rate, mg/h | increased | 13 | 0 | 0 | 0.66 |
| | normal | 22 | 1 | 1 | |
| | reduced | 37 | 2 | 4 | |
| $K^+$, mmol/l | increased | 29 | 0 | 1 | 0.57 |
| | normal | 33 | 2 | 3 | |
| | reduced | 10 | 1 | 1 | |
| NANA, μM/l | increased | 72 | 3 | 5 | 1.00 |
| | normal | 0 | 0 | 0 | |
| | reduced | 0 | 0 | 0 | |
| $Na^+$, mmol/l | increased | 11 | 2 | 2 | 0.04* |
| | normal | 61 | 1 | 3 | |
| | reduced | 0 | 0 | 0 | |

**Note.** * - statistically significant relationship between the content of the indicator in the basal secretion and the value of hydrogen ion flow after stimulation.

According to the results of the post-stimulation secretion tests, all cases were divided into three groups according to the degree of secretion: corresponding to the particular reference value (3.75 %), higher (90.0 %) and lower (6.25 %) than it.

It was found that in the group with normal $Na^+$ levels, pentagastrin stimulation in 94.0 % of cases led to ultra-high $H^+$ efflux compared with the reference values; in the group with reduced $Na^+$ levels (none); in the group with increased $Na^+$ - 73.0 % of patients after pentagastrin stimulation had higher $H^+$ efflux than the reference values.

Thus, an inverse (reverse, negative) significant relationship ($p = 0.04$) was found between the $Na^+$ content in basal secretion and $H^+$ debit after pentagastrin administration.

As for the other analyzed parameters, the results of the $\chi^2$-test did not reveal any significant relationships between the content of these parameters in basal secretion and $H^+$ debit after pentagastrin administration.

However, as a result of further statistical analysis, all possible constellations of gastric juice parameters were analyzed, and the optimal constellations for predicting hyperacidity, normacidity and hypoacidity after submaximal pentagastrin stimulation were searched for on the basis of the lowest *p*-value in the z-test for each possible constellation (Table 3).

*Table 3*

**Optimal constellations for predicting the response of the parietal cells to stimulation (parameters; %; *p*)**

| Acidity | Constellation | Proportion of people with constellation, % | Part among all other persons, % | *p* |
|---|---|---|---|---|
| Hyperacidity | $Na^+$ normal and NANA higher than normal | 94.0 | 73.0 | 0.02* |
| Normacidity | $Na^+$ above normal and NANA above normal and $K^+$ below normal and pepsin flow rate below normal and pepsin below normal and total acidity below normal range | 100.0 | 3.0 | <0.01* |
| Hypoacidity | Free HCI below normal and $H^+$ flow rate below normal and pepsin normal and pepsin flow rate below normal and $K^+$ above normal and $Na^+$ | 100.0 | 5.0 | <0.01* |

**Note.** * - statistically significant difference between the proportion of people with a response to stimulation among those who fall into the constellation and corresponding proportion among all others.

It was found that the best constant for predicting hyperacidity is the value of basal secretion parameters ($Na^+$ normal, NANA above normal) - 94.0 % of such patients have a $H^+$ debit above normal after submaximal pentagastrin stimulation compared to 73.0 % of all other patients ($p = 0.02$). The best constant for predicting normacidity is the value of basal secretion parameters ($Na^+$ above normal, NANA above normal, $K^+$ below normal, pepsin debitage below normal, pepsin below normal, total acidity below normal) - 100.0 % of such patients have a normal $H^+$ debitage after submaximal pentagastrin stimulation compared to 3.0 % of all other patients ($p < 0.01$). The best constant for predicting hypoacidity is the value of basal secretion parameters ($Na^+$ normal, $K^+$ above normal, pepsin debit below normal, pepsin normal, $H^+$ debit below normal, HCl below normal) - 100.0 % of such patients have a $H^+$ debit below normal after submaximal pentagastrin stimulation compared to 5.0 % all other patients ($p < 0.01$).

At the third stage of the study, after the administration of an $H_2$-blocker of histamine receptors, the results presented in Table 4 were obtained.

*Table 4*

**Average values of hydrogen ion flow in the studied subgroups and the whole sample after blocking (parameters; average value of hydrogen ion flow)**

| Parameter | Group by content of the parameter | Average $H^+$ flow rate, mmol/h | | |
|---|---|---|---|---|
| | | Patients with hyperacidity | Patients with normalcy | Patients with hypoacidity |
| Amount of gastric juice, ml | enlarged | - | - | - |
| | normal | 18.4 | - | 0.4 |
| | reduced | 21.8 | 4.7* | 5.5* |
| Free HCl, mmol/l | enlarged | 35.7* | - | - |
| | normal | 13.3 | - | - |
| | reduced | 21.6 | 4.7* | 4.5* |
| Total acidity, mmol/l | enlarged | 35.7* | - | - |
| | normal | 12.8* | - | - |
| | reduced | 21.4 | 4.7* | 4.5* |
| $H^+$ flow rate, mmol/h | enlarged | 21.1 | 3.8* | 1.6* |
| | normal | 22.9 | 6.7 | 10.5 |
| | reduced | 18.1 | - | 4.5* |
| Pepsin, mg/l | enlarged | 24.5 | 2.7 | - |
| | normal | 18.1 | - | 4.6* |
| | reduced | 20.2 | 5.8* | 4.4* |
| Pepsin flow rate, mg/h | enlarged | 25.8 | - | - |
| | normal | 19.1 | 2.7 | 0.4 |
| | reduced | 19.7 | 5.8* | 5.5* |
| $K^+$, mmol/l | enlarged | 20.0 | - | 8.8 |
| | normal | 22.4 | 3.8* | 1.1* |
| | reduced | 16.6 | 6.7 | 10.5 |
| NANA, μM/l | enlarged | 20.6 | 4.7* | 4.5* |
| | normal | - | - | - |
| | reduced | - | - | - |
| $Na^+$, mmol/l | enlarged | 16.7 | 5.8* | 0.3* |
| | normal | 21.4 | 2.7 | 7.3* |
| | reduced | - | - | - |
| Total number of patients | | 19 | | |

**Note.** * - statistically significant difference between the mean value of hydrogen ion flow rate in the subgroup and the mean value of hydrogen ion flow rate in the entire sample.

After statistical analysis of the response of hydrogen ion flow rate to blockade, several regularities were established. For patients with $H^+$ debit below normal after submaximal pentagastrin stimulation, 9 groups showed a significantly lower $H^+$ debitage after blockade compared with the average $H^+$ debitage after blockade for the entire sample: for patients with decreased basal secretion juice content, for patients with decreased basal secretion HCl, for patients with decreased basal secretion total acidity, for patients with increased basal secretion $H^+$ flow, for patients with decreased pepsin flow rate in basal secretion, for patients with normal $K^+$ content in basal secretion, for patients with increased NANA content in basal secretion, for patients with normal $Na^+$ content in basal secretion, for patients with increased $Na^+$ content in basal secretion

For patients with a normal $H^+$ flow rate after submaximal pentagastrin stimulation, 9 groups (not all coincide with the previous 9 groups) recorded significantly lower values of $H^+$ flow rate after the blocker compared with the average $H^+$ flow rate after the blocker for the entire sample: for patients with decreased amount of juice in basal secretion, for patients with decreased HCl in basal secretion, for patients with decreased total acidity in basal secretion, for patients with increased $H^+$ flow in basal secretion, for patients with decreased pepsin concentration in basal secretion, for patients with decreased pepsin flow rate in basal secretion, for patients with normal $K^+$ content in basal secretion, for patients with increased NANA content in basal secretion, for patients with increased $Na^+$ ion concentration in basal secretion.

For patients with higher than normal $H^+$ flow rate after submaximal pentagastrin stimulation, the response to the $H_2$-histamine receptor blocker was twofold. For the two analyzed subgroups, a significantly higher $H^+$ flow rate after the blocker was recorded compared with the average $H^+$ flow rate after the blocker for the entire sample, in particular, for patients with increased HCl content in basal secretion and for patients with increased total acidity in basal secretion.

In contrast, for patients with higher than normal $H^+$ flow rate after submaximal pentagastrin stimulation, one analyzed subgroup showed a significantly lower $H^+$ flow rate after the blocker compared with the average $H^+$ flow rate after the blocker for the entire sample: patients with normal total basal acidity.

All possible constellations for predicting the response of the parietal cells to blockade were analyzed, and the best constellation for predicting a strong and weak response to blockade was identified by the criterion of the lowest *p*-value among all possible constellations (Table 5).

*Table 5*

**The best constellations for predicting the response of the parietal glands to blockade (parameters; mean value of hydrogen ion flow; *p*)**

| Reaction | Constellation | Average value for people with constellation | *p* |
|---|---|---|---|
| 1 | 2 | 3 | *4* |
| Strong | NANA above normal and $K^+$ | 0.5 | <0.01* |
| | normal, pepsin flow rate normal, pepsin normal, $Na^+$ above normal | | |
| Weak | The amount of gastric juice is less than normal and free HCI is less than normal, pepsin is higher than normal, pepsin flow rate higher than normal, $K^+$ higher than normal, $Na^+$ normal | 43.15 | 0.01* |

*Contin of the Table 5*

**Note.** * - statistically significant difference between the mean value of hydrogen ion flow for individuals with constellation and the mean value of hydrogen ion flow in the entire sample.

The best constellation for predicting a strong response to a blocker is the value of basal secretion parameters (NANA above normal, $K^+$ normal, pepsin normal, pepsin normal, $Na^+$ above normal) - the mean value of hydrogen ion debit after blocking for patients with this constellation is 0.5, which is significantly less than the mean value of $H^+$ debit for all patients after blocking - 19 (*p*-value <0.01). The best constellation for predicting a weak response to a blocker is the value of basal secretion parameters (gastric juice less than normal, free HCI below normal, pepsin above normal, pepsin flow rate above normal, $K^+$ above normal, $Na^+$ normal) - the mean value of hydrogen ion flow rate after blocking with this constellation is 43.15, which is significantly higher than the average value of $H^+$ debit for all patients after blocking - 19 ($p = 0.01$).

The practical value of the results obtained is the possibility of selecting a higher dosage of the blocker for patients who are predicted to have a mild reaction, and a lower dosage for patients who are predicted to have a strong reaction.

**Conclusions.** The $H^+$ flow rate in basal secretion is in a reliable direct correlation with the following indicators in basal secretion: total acidity ($r = 0.87$, $p < 0.01$), free HCl ($r = 0.85$, $p < 0.01$), pepsin flow rate ($r = 0.51$, $p < 0.01$), gastric juice quantity ($r = 0.44$, $p < 0.01$), and pepsin concentration ($r = 0.25$, $p = 0.03$). Hyperacidity after stimulation occurred most often in patients with normal basal $Na^+$ (94.0 % vs. 73.0 % in all other patients, $p = 0.02$). Normacidity after stimulation most often occurred in patients with $Na^+$ above normal in combination with $K^+$ below normal, pepsin debit below normal, pepsin below normal, total acidity below normal in basal secretion (100.0 % vs. 3.0 % among all others, $p = 0.0000003$). Hypoacidity after stimulation most often occurred in patients with normal $Na^+$, $K^+$ above normal, pepsin debit below normal, pepsin content below normal, $H^+$ debit below normal, HCl below normal in basal secretion (100.0 % vs. 5.0 % among all others, $p = 0.0001$).

A significantly weak response to the $H_2$-blocker was confirmed for patients with hyperacidity after stimulation

in combination with increased HCl content, increased total acidity in basal secretion. A significantly strong response to $H_2$-blockers has been confirmed for patients with hyperacidity after stimulation in combination with total basal acidity within the normal range, as well as for patients with normacidity or hypoacidity after stimulation in combination with decreased gastric juice content, decreased HCI content, decreased total acidity, increased $H^+$ flow, decreased pepsin flow, normal $K^+$ content, and increased $Na^+$ content in basal secretion:

Additionally, the significantly strong response to $H_2$-blockers was confirmed for patients with hypoacidity after stimulation in combination with normal basal secretion $Na^+$, as well as for patients with normacidity after stimulation in whom the basal secretion pepsin concentration was reduced. The best constellation for predicting a strong response to a blocker ($p < 0.01$) involves the following values of basal secretion parameters (NANA above normal and $K^+$ above normal, pepsin flow rate above normal, pepsin above normal, $Na^+$ above normal), and the best constellation for predicting a weak response to a blocker ($p = 0.01$ - amount of gastric juice is below normal, free HCI is below normal, pepsin is above normal, pepsin flow rate is above normal, $K^+$ is above normal, $Na^+$ is normal (in basal secretion).

**References**


1. Дзюбановський ІЯ, Війтович ЛЄ. Неускладнена виразкова хвороба шлунка: прогнозування перебігу і лікувальна тактика. Шпитальна хірургія. Журнал імені Л. Я. Ковальчука. 2016;3:101–103. (Dziubanovskyi IYa, Viytovych LYe. Uncomplicated gastric ulcer: Prediction of the course and treatment tactics. Hospital Surgery. Journal Named After LY Kovalchuk. 2016;3:101-103).
2. Завгородній ІВ, Сирова ГО, Ткачук НМ та ін. Медична хімія. Навчальний посібник, рекомендований МОЗ та МОН України як навчальний посібник для самостійної роботи студентів вищих медичних навчальних закладів IV рівня акредитації. Харків: ХНМУ, 2010. – 268 с. (Zavgorodniy IV, Syrova GO, Tkachuk NM et al. Medical chemistry. Kharkiv: KHNMU; 2010. 268 p.).
3. Калібабчук ВО, Чекман ІС, Галинська ВІ та ін.; за ред. проф. В.О. Калібабчук. Медична хімія: підручник. Київ: Медицина; 2013. 336 с. (Kalibabchuk VO, Chekman IS, Galinska VI et al. Medical chemistry: textbook. Kalibabchuk VO, editor. Kyiv: Medicine; 2013. 336 p.).
4. Коркушко ОВ, Шатило БВ, Наскалова СС, Гавалко ЮВ, Романенко МС, Стаднюк ЛА, Руденко АІ. Функціональний стан шлункових залоз у здорових людей літнього віку за результатами дослідження базальної та стимульованої пентагастрином секреції. Сучасна гастроентерологія. 2008; 3(41):14–20. (Korkushko OV, Shatilo BV, Naskalova SS, Havalko YV, Romanenko MS, Stadnyuk LA, Rudenko AI. Functional state of the gastric glands in healthy elderly people based on the results of basal and pentagastrin-stimulated secretion. Modern Gastroenterology. 2008;3(41):14-20).
5. Левітін ЄЯ, Бризицька АМ, Клюєва РГ. Загальна та неорганічна хімія. Вінниця: Нова книга; 2003. 464 с. (Levitin EY, Bryzytska AM, Klyueva RG. General and inorganic chemistry. Vinnytsia: New Book; 2003. 464 p.).
6. Скляров ЄЯ, Скляров ОЯ. Гіістамін-простагландиновий тест для оцінки дії поротекторів при деяких захворюваннях шлунка. Науково-медичні аспекти фізіології: рекомендації для студентів і наукових співробітників-фізіологів. Львів. 1989. 31 с. (Sklyarov EY, Sklyarov OY. Hyistamine-prostaglandin test for evaluation of the action of potentiators in some diseases of the stomach. Scientific and medical aspects of physiology: Recommendations for students and researchers-physiologists. Lviv; 1989. 31 p.).
7. Фадєєнко ГД, Нікіфорова Я В. Можливості ерадикації *Helicobacter pylori* на основі сучасних рекомендацій Маастрихта VI/Флорентійського консенсусу у світі та Україні. Сучасна гастроентерологія. 2024;2:90–96. (Fadeenko GD, Nikiforova YV. Possibilities of *Helicobacter pylori* eradication based on modern recommendations of Maastricht VI/Florence Consensus in the world and Ukraine. Modern Gastroenterology. 2024;2:90-96).
8. Allen A, Flemström G. Gastroduodenal mucus bicarbonate barrier: protection against acid and pepsin. Am J Physiol Cell Physiol. 2005;288(1):C1-C19. doi:10.1152/ajpcell.00102.2004
9. Almadi MA, Lu Y, Alali AA, Barkun AN. Peptic ulcer disease. Lancet. 2023;404(10397):68-81.
10. Begg M, Tarhuni M, Fotso MN, Gonzalez NA, Sanivarapu RR, Osman U et al. Comparing the safety and efficacy of proton pump inhibitors and histamine-2 receptor antagonists in the management of patients with peptic ulcer disease: A Systematic Review. Cureus. 2023;15(8):e44341. doi:10.7759/cureus.44341
11. Bisswanger H. Enzyme Assays. Perspect Sci. 2014;1:41-55.
12. Brzozowski T, Magierowska K, Magierowski M, Ptak-Belwska A, Pajdo R, Kwiecien S et al. Recent advances in the gastric mucosal defence against stress induced gastric lesions. Importance of renin-angiotensin vasoactive metabolites, gaseous mediators and appetite peptides. Curr Pharm Des. 2017;23(27):3910-3922. doi:10.2174/1381612823666170220160222
13. Bychkov MA, Bychkova SV, Shvydkyy YB, Bychkov YA. Efficiency of differential diagnosis of gastroesophageal reflux disease according to calcium salivary content. Exp Clin Physiol Biochem. 2014;2(66):86-91.
14. Bychkov MA, Bychkov YA, Bychkova SV. The value of non-invasive diagnostic methods for gastroesophageal reflux disease. Ukr Med J. 2013;5(97):124-126.
15. Ergun P, Kipcak S, Dettmar PW, Fisher J, Woodcock AD, Bor S. Pepsin and pH of Gastric Juice in Patients With Gastrointestinal Reflux Disease and Subgroups. J Clin Gastroenterol. 2022;56(6):512-517. doi:10.1097/MCG.0000000000001560
16. Freedman D, Pisani R, Purves R. Statistics. 4th ed. New York: W.W. Norton & Company; 2007.
17. Fisher RA. On the interpretation of $\chi^2$ from contingency tables, and the calculation of P. J R Stat Soc. 1922;85(1):87-94. doi:10.2307/2340521
18. Geibel JP. Role of potassium in acid secretion. World J Gastroenterol. 2005;11(34):5259-5265. doi:10.3748/wjg.v11.i34.5259
19. Jukic I, Rusic D, Vukovic J, Zivkovic PM, Bukic J, Leskur D et al. Correlation of registered drug packs with Maastricht V/Florence Consensus Report and national treatment guidelines for management of Helicobacter pylori infection. Basic Clin Pharmacol Toxicol. 2020;126(3):212-225. doi:10.1111/bcpt.13322

20. Ito T, Ramos-Alvarez I, Jensen RT. Long-term proton pump inhibitor-acid suppressive treatment can cause vitamin B12 deficiency in Zollinger-Ellison syndrome (ZES) patients. Int J Mol Sci. 2024;25(13):7286. doi:10.3390/ijms25137286
21. Kavitt RT, Lipowska AM, Anyane-Yeboa A, Gralnek IM. Diagnosis and treatment of peptic ulcer disease. Am J Med. 2019;132(4):447-456. doi:10.1016/j.amjmed.2018.12.009
22. Nishiyama K, Muka T. Sialic acid impact on the gut microbiome and function. Glycoforum. 2022;25(2):A3.
23. Lewis OL, Keener JP, Fogelson A. A physics-based model for the maintenance of the pH gradient in the gastric mucus layer. Am J Physiol Gastrointest Liver Physiol. 2017;313(6):G599-G612. doi:10.1152/ajpgi.00221.2017
24. Litou C, Psachoulias D, Vertzoni M, Dressman J, Reppas C. Measuring pH and buffer capacity in fluids aspirated from the fasted upper gastrointestinal tract of healthy adults. Pharm Res. 2020;37(3):42. doi:10.1007/s11095-0192731-3
25. Martinsen TC, Fossmark R, Waldum HL. The phylogeny and biological function of gastric juice - Microbiological consequences of removing gastric acid. Int J Mol Sci. 2019;20(23):6031. doi:10.3390/ijms20236031
26. Pelin E, Kipcak S, Dettmar PW, Fisher J, Woodcock AD, Bor S. Pepsin and pH of gastric juice in patients with gastrointestinal reflux disease and subgroups. J Clin Gastroenterol. 2022;56(6):512-517. doi:10.1097/MCG.0000000000001560
27. Petersen KU. Pepsin and its importance for functional dyspepsia: Relic, regulator or remedy? Dig Dis. 2018;36(2):98-105. doi:10.1159/000481399
28. Pounder RE, Fraser AG. Gastric acid secretion and intragastric acidity: Measurement in health and disease. Baillieres Clin Gastroenterol. 1993;7(1):55-80. doi:10.1016/0950-3528(93)90031-M
29. Rice JA. Mathematical Statistics and Data Analysis. 3rd ed. Belmont: Duxbury Advanced; 2006.
30. Roberts NB. Review article: Human pepsins - their multiplicity, function and role in reflux disease. Aliment Pharmacol Ther. 2006;24(Supp. 2):2-9.
31. Yusuf S, Nok AJ, Ameh DA. Correlation of gastric mucosal damage with sialic acid profile in rats: Effect of hydrochloric acid, pepsin and hypertonic saline. Cell Biochem Funct. 2005;23(5):339-345.
32. Sharaev PN. Determination of sialic acids by resorcinol method. Clin Lab Diagnosis. 1990;(11):38-40.
33. Sprinthall RC. Basic statistical analysis. 9th ed. Boston: Pearson Education; 2011.
34. Svennerholm L. Quantitative estimation of sialic acids. II. A colourimetric resorcinol-hydrochloric acid method. Biochim Biophys Acta. 1957;24:604-611. doi:10.1016/0006-3002(57)90254-8
35. Tin VP. Method for determination of pepsin in gastric juice using colourimetry. Clin Lab Diagnosis. 1986;(11):656-657.
36. Vakil N. Peptic ulcer disease: A review. JAMA. 2024;332(21):1832-1842. doi:10.1001/jama.2024.19094
37. van Diepen S, Coulson T, Wang X, Opgenorth D, Zuege DJ, Harris J et al. Efficacy and safety of proton pump inhibitors versus histamine-2 receptor blockers in the cardiac surgical population: insights from the PEPTIC trial. Eur J Cardiothorac Surg. 2022;62(2):ezac124. doi:10.1093/ejcts/ezac124
38. Varki A. Sialic acids in human health and disease. Trends Mol Med. 2008;14(8):351-360.
39. Cho YK, Choi MG, Choi SC, Lee IS, Kim SW, Choi KY et al. Randomised clinical trial: Tegoprazan, a novel potassium-competitive acid blocker, or lansoprazole in the treatment of gastric ulcer. Aliment Pharmacol Ther. 2020;52(5):789-797. doi:10.1111/apt.15865
40. Yuksel ES, Hong S, Strugala V, Slaughter JC, Goutte M, Garrett CG et al. Rapid salivary pepsin test: Blinded assessment of test performance in gastroesophageal reflux disease. Laryngoscope. 2012;122(6):1312-1316.
41. Zullo A, Annibale B, Dinis-Ribeiro M, Fanchellucci G, Esposito G, Hassan C. Gastric juice analysis in clinical practice: Why, how, and when. The experience with EndoFaster. Eur J Gastroenterol Hepatol. 2024;36(3):264-270. doi:10.1097/MEG.0000000000002704
42. Zullo A, Germanà B, Galliani E, Iori A, de Pretis G, Pastore M et al. Real-time determination of gastric juice pH with EndoFaster for atrophic gastritis assessment. Dig Liver Dis. 2022;54(12):1646-1648. doi:10.1016/j.dld.2022.06.014

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**Conflict of interests**
The authors declare no conflict of interests.

# Predictive Value of Individual Gastric Secretion Indices and Their Constellations for Predicting the Response of Gastric Mucosal Parietal Cells to Pentagastrin Stimulation and Famotidine Blocking Effect in Patients with Gastric and Duodenal Ulcers

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**Introduction.** Evaluating acid-reducing medications through their effect on various gastric juice parameters in peptic ulcer patients provides deeper insight into the complex mechanism of gastric secretion, which includes acidity levels, pepsin, electrolytes, bicarbonates, and mucus.

**The aim of the study.** To determine the prognostic value of gastric secretion parameters and their constellations for predicting parietal cell response to submaximal pentagastrin stimulation and the blocking effect of famotidine in patients with gastric and duodenal peptic ulcer disease.

**Materials and methods.** The study included 40 randomized Helicobacter pylori-positive patients (28 women, 12 men, aged 18-68) with endoscopically confirmed duodenal ulcer disease in the acute phase. Modified fractional probing was used to assess changes in gastric secretion.

**Results.** $H^+$ debit in basal secretion showed a significant direct correlation with multiple parameters. Different acid responses to stimulation were associated with specific baseline parameter constellations. Weak response to $H_2$-blocker was confirmed in patients with hyperacidity after stimulation, combined with elevated HCl and increased total acidity in basal secretion. A strong response to $H_2$-blocker was confirmed in several parameter constellations, with the best predictive constellation ($p < 0.01$) including elevated N-acetylneuraminic acid, normal $K^+$, normal pepsin debit, normal pepsin, and elevated $Na^+$ in basal secretion.

**Conclusions.** The prognostic value of gastric secretion parameters and their constellations allows tailoring blocker dosage: higher doses for patients predicted to have a weak response and lower doses for those predicted to have a strong response to stimulation.

**Keywords:** gastric secretion, peptic ulcer, hydrochloric acid, proton pump inhibitors, $H_2$-histamine receptor blockers.

# Прогнозна цінність окремих показників шлункової секреції та їхніх констеляцій для передбачення реакції парієтальних клітин слизової оболонки шлунка на стимулювання пентагастрином і блокувальну дію фамотидину у хворих на виразкову хворобу шлунка та дванадцятипалої кишки

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**Вступ.** Оцінка дії кислотознижувального лікарського засобу через його вплив на цілу низку показників шлункового соку у хворих на виразкову хворобу шлунка та дванадцятипалої кишки уможливлює значно глибше охарактеризувати його вплив на складний механізм шлункової секреції. Цей механізм містить показник не лише кислотности, а й концентрації пепсину, електролітів, гідрокарбонатів і слизу. Виявлення цих взаємозв'язків (констеляцій) уможливлює на основі вихідних показників шлункової секреції та реакції на стимуляцію передбачити ефективність конкретного лікарського засобу та індивідуально визначити його дозування.

**Мета.** З'ясувати прогнозну цінність окремих показників шлункової секреції (кількість шлункового соку, вільна соляна кислота, загальна кислотність, дебіт водневих йонів, пепсин, дебіт пепсину, показник йонів калію у шлунковому соці, N-ацетилнейрамінова кислота в соці, йони натрію в соці) та їхніх констеляцій для передбачення реакції парієтальних клітин слизової оболонки шлунка на субмаксимальне стимулювання пентагастрином і дію блокатора $H_2$-гістамінових рецепторів фамотидину у хворих на виразкову хворобу шлунка та дванадцятипалої кишки.

**Матеріяли й методи.** Отримавши письмову згоду пацієнтів на проведення обстеження, в рандомізований спосіб із попередньою стратифікацією за наявністю ендоскопічно підтвердженого діягнозу виразкова хвороба шлунка і дванадцятипалої кишки у фазі загострення до дослідження залучили 40 пацієнтів (28 жінок і 12 чоловіків віком 18–68 років) на базі 5-ї міської лікарні м. Львова. Усі пацієнти, які брали участь у дослідженні, мали позитивний уреазний тест на наявність Helicobacter pylori.

Для оцінки зміни шлункової секреції під впливом субмаксимальної стимуляції пентагастрином і наступним уведенням $H_2$-блокатора гістамінових рецепторів фамотидину використовували методику фракційного зондування у модифікованому варіянті.

**Результати.** Дебіт $H^+$ у базальній секреції перебуває у достовірному прямому кореляційному зв'язку із такими показниками в базальній секреції: загальною кислотністю ($r = 0,87$, $p < 0,01$), вільною HCl ($r = 0,85$, $p < 0,01$), із дебітом пепсину ($r = 0,51$, $p < 0,01$), із об'ємом шлункового соку ($r = 0,44$, $p < 0,01$), концентрацією пепсину ($r = 0,25$, $p = 0,03$). Гіперацидність після стимуляції найчастіше виникала у пацієнтів із $Na^+$ у нормі в базальній секреції (94,0 % проти 73,0 % серед усіх інших, $p = 0,02$). Нормацидність після стимуляції найчастіше виникала у пацієнтів із $Na^+$ вище норми у поєднанні із $K^+$ нижче норми, дебітом пепсину нижче норми, пепсином нижче норми, загальною кислотністю нижче норми в базальній секреції (100,0 % проти 3,0 % серед усіх інших, $p = 0,0000003$). Гіпоацидність після стимуляції найчастіше виникала у пацієнтів із $Na^+$ в нормі, $K^+$ вище норми, дебітом пепсину нижче норми, вмістом пепсину у нормі, дебітом $H^+$ нижче норми, HCl нижче норми в базальній секреції (100,0 % проти 5,0 % серед усіх інших, $p = 0,0001$).

Достовірно слабка реакція на $H_2$-блокатор підтверджена для пацієнтів із гіперацидністю після стимуляції у поєднанні зі збільшеним вмістом HCl, підвищеною загальною кислотністю в базальній секреції. Достовірно сильна реакція на $H_2$-блокатор підтверджена для пацієнтів із гіперацидністю після стимуляції у поєднанні зі загальною кислотністю в базальній секреції в межах норми, а також для пацієнтів із нормацидністю або гіпоацидністю після стимуляції у поєднанні зі зменшеним вмістом шлункового соку, зменшеним вмістом HCI, зниженою загальною кислотністю, підвищеним дебітом $H^+$, зниженим дебітом пепсину, нормальним вмістом $K^+$, підвищеним вмістом $Na^+$ у базальній секреції.

Додатково достовірно сильна реакція на $H_2$-блокатор підтверджена для пацієнтів із гіпоацидністю після стимуляції у поєднанні з нормальним вмістом $Na^+$ у базальній секреції, а також для пацієнтів із нормацидністю після стимуляції, у яких концентрація пепсину в базальній секреції була знижена. Оптимальна констеляція для прогнозування сильної реакції на блокатор ($p < 0,01$) передбачає такі значення показників у базальній секреції (вміст N- ацетилнейрамінової кислоти більше норми, $K^+$ у нормі, дебіт пепсину в нормі, пепсин в нормі, $Na^+$ вище норми), оптимальна констеляція для прогнозування слабкої реакції на блокатор ($p = 0,01$ – кількість шлункового соку нижче норми, вільна HCI нижче норми, пепсин вище норми, дебіт пепсину вище норми, $K^+$ вище норми, $Na^+$ у нормі (в базальній секреції).

**Висновки.** Прогнозна цінність окремих показників шлункової секреції та їхніх констеляцій для передбачення реакції парієтальних клітин слизової оболонки шлунка на субмаксимальне стимулювання пентагастрином і дію блокатора $H_2$-гістамінових рецепторів фамотидину у хворих на виразкову хворобу шлунка та дванадцятипалої кишки уможливлює дібрати більше дозування блокатора для пацієнтів, для яких прогнозується слабка реакція, і меншого – для пацієнтів, для яких прогнозується сильна реакція на стимулювання.

**Ключові слова:** шлункова секреція, пептична виразка, соляна кислота, інгібітори протонної помпи, блокатори $H_2$-гістамінових рецепторів.

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