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THE EFFECT OF PROTON PUMP INHIBITORS ON FORMATION OF INACTIVE (COCCOID) FORMS OF *H. PYLORI* INFECTION

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Key words: proton pump inhibitors; helicobacter infection; coccoid form

The comprehensive study of 62 patients with chronic helicobacteriosis, who took PPIs (the course of PPI administration was from 1 to 3 days) the day before the examination, has been conducted. When testing after PPI administration during 1 day HP infection was found in 100% of cases, but only in an inactive coccoid form with a high degree of contamination of the gastric mucosa (on the average it is higher (+ +)) with no significant difference (p>0.05) of this index over topographic areas. When analyzing this index over the same topographic areas in relation to the course of PPI administration there is a reliable reduction (p<0.05) of the HP concentration in all areas each day except the middle third of the gastric corpus by the lesser curvature where we can see only a tendency of reduction of the HP concentration on the gastric mucosa. On the third day of PPI administration the reliably highest concentration of HP is still on the mucosa in the middle third of the gastric corpus by the lesser curvature (p<0.05). The use of proton pump inhibitors in monotherapy promotes a rapid conversion of active forms of HP infection into inactive coccoid forms across the gastric mucosa. Reduction of HP infection on the gastric mucosa occurs due to the natural washing of bacteria when eating and drinking to the intestine and it may contribute to the formation of the fecal-oral route.

Beginning from 1996 when the first Maastricht Consensus in the treatment of chronic helicobacteriosis was created, the main drugs in all schemes till now are proton pump inhibitors (PPI) designed not only to reduce the acidity level of the gastric juice as the aggression factor, but also to help the antibiotics to realize their potential in fighting against *Helicobacter pylori* (HP) [2, 3]. But antibiotics act only on the active form of HP and only in the stage of mitosis [3]. The lack of data in the available literature on the impact of PPI on HP in monotherapy with these drugs was the reason for our work.

Materials and Methods

The comprehensive study of 62 patients with chronic helicobacteriosis, who took PPIs (the course of PPI administration was from 1 to 3 days) the day before the examination, has been conducted. The age of patients varied from 17 to 63 years old (the average age was 36.2±0.19 years old); among them there were 39 men (62.9%) and 23 women (37.1%). The comprehensive examination of the patients included: step by step intraventricular pH-metry by the method of Chernobrovy V.N. [7]; esophagogastroduodenoscopy (EPGDS) by the common method [5], double testing on HP-infection (rapid urease test and microscopy of stained Gyms smears), for which the biopsic material was taken from 4 topographic areas of the stomach: from the middle third of the antrum and the gastric corpus by the greater and lesser curvature, according to our methodology [1], as well as the histologic examination of the gastric mucosa of these areas according to the latest classification [6].

The examination sequence was as follows: at first pH-metry was carried out, then EPGDS with biopsy sampling was performed to test for HP and histologic study of the gastric mucosa. The examination was made in the morning in the fasted state in 12-14 hours after the last meal. The data obtained were processed statistically with the help of Student t-test with calculation of mean values (M) and evaluation of probability of deviations. Changes were supposed to be reliable at p<0.05. The statistic calculations were perfomed with the help of Excel spreadsheets for Microsoft Office.

Results and Discussion

When determining the acidity level there were levels corresponded to normal acidity – in 18 (29%) cases, moderate hypoacidity – in 20 (32.3%) cases, expressed hypoacidity – in 24 (38.7%) cases. When conducting EPGDS and histologic study of the gastric mucosa the existence of chronic gastritis both in active and non-active forms was confirmed among 100% of patients.

When testing HP infection was found in 100% of cases, but only in a non-active coccoid form. The data of contamination degree of the gastric mucosa by HP infection by the topographic area of the stomach with different course of PPI administration are given in Table.

When analyzing the data obtained concerning the degree of the gastric mucosa contamination by HP infection there is the absence of significant difference of

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Table

Degree of *Helicobacter pylori* infection contamination of the gastric mucosa by the topographic areas with different course of proton pump inhibitors administration (n = 62)

The course of PPI administration	Topographic area of the stomach			
	Antrum (M±m) / (+)		Gastric corpus (M±m) / (+)	
	Greater curvature	Lesser curvature	Greater curvature	Lesser curvature
1st day (n = 21)	2.13±0.11	2.12±0.11	2.11±0.11	2.10±0.11
2nd day (n = 19)	1.24±0.12	1.22±0.12	1.87±0.12	1.93±0.12
3rd day (n = 22)	0.80±0.11	0.81±0.11	1.34±0.11	1.78±0.11

Note: n – is the number of examinations.

this index over topographic areas after PPI administration during a day. When analyzing this index over the same topographic areas in relation to the course of PPI administration there is a reliable reduction ($p<0.05$) of the HP concentration in all areas each day except the middle third of the gastric corpus by the lesser curvature where we can see only a tendency of reduction of the HP concentration on the gastric mucosa. When analyzing the changes of mucosa contamination degree of different topographic areas of the stomach on the 2nd day of PPI administration a reliable lower concentration of HP ($p<0.05$) in the antrum is observed in relation to the gastric corpus both by the greater and lesser curvature, while there are no reliable differences in the gastric corpus ($p>0.05$). On the 3rd day of PPI administration the highest concentration of HP is still on the mucosa in the middle third of the gastric corpus by the lesser curvature ($p<0.05$).

These results can be interpreted from 2 positions. From the viewpoint of some scientists with decrease of the acidity level under the effect of PPI HP infection migrates from the antrum of the stomach to the gastric corpus where acidity remains higher and where helicobacter infection have a chance for survival since the absence of acid is fatal to it because of the peculiarities of getting energy for this bacterium [4]. However, the data obtained demolish this view because after the 1st day of PPI administration the HP concentration is equal in all parts of the stomach and it is high everywhere (on the average it is higher (++)) and HP is only as fixed non-active coccoid forms, which are the form of protection under unfavourable environmental conditions, while only active forms of bacteria have mobility and ability to migration and live on the gastric mucosa [2, 4]. That is why reduction of the HP infection level during 3 days of PPI administration, from our point of view, occurs due to the natural washing of these forms when eating and drinking from the gastric mucosa, whereupon non-active forms get to the intestine and eliminate with feces forming the fecal-oral route. Such mechanism was confirmed experimentally when for obtaining non-active forms of other kind of helibacteria infections – *Helicobacter mustelae* living on the ferret's gastric mucosa proton pump inhibitors were injected to animals [2]. The middle third of the gastric corpus by the lesser curvature is the least compact area for different negative factors in relation to HP, therefore, it is the site where helicobacter infection adapted to the new acidity level, transfers again to the active form and forms an intracellular "depot", which can be the future recurrence of the disease [8].

From our point of view, antibiotics, which according to general schemes are used together with PPI, do not act as "killers" of HP, but more than likely as factors, which do not allow the inactive form of bacteria to pass into the active form and promote releasing of coccoid forms in the environment; in turn, it increases the risk of re-infection of patients and their family because now it is common practice to treat chronic gastritis and peptic ulcer at home [3]. De-Nol, a bismuth drug introduced already to the first-line therapy, is the only drug that kills both active and non-active forms of HP and until now any bacteria do not have resistance to it [5].

CONCLUSIONS

1. The use of proton pump inhibitors in monotherapy promotes a rapid conversion of active forms of HP infection into inactive coccoid forms across the gastric mucosa.

2. Reduction of HP infection on the gastric mucosa occurs due to the natural washing of bacteria when eating and drinking to the intestine and it may contribute to the formation of the fecal-oral route.

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ВПЛИВ ІНГІБІТОРІВ ПРОТОННОЇ ПОМПИ НА ФОРМУВАННЯ НЕАКТИВНИХ (КОКОПОДІБНИХ) ФОРМ ГЕЛІКОБАКТЕРНОЇ ІНФЕКЦІЇ

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Ключові слова: інгібітори протонної помпи; гелікобактерна інфекція; кокоподібні форми

Було комплексно обстежено 62 хворих на хронічний гелікобактеріоз, які напередодні обстеження приймали інгібітори протонної помпи (ІПП) (тривалість прийому – від 1 до 3-х діб). При тестуванні після прийому ІПП протягом 1 доби НР-інфекція була виявлена в 100% випадків, однак в неактивній кокоподібній формі при високому ступені обсіменіння слизової шлунка (у середньому більше (+ +)) за відсутності достовірної відмінності (p > 0,05) даного показника по топографічних зонах. При аналізі даного показника по одних і тих же топографічних зонах щодо тривалості прийому ІПП відзначається достовірне (p < 0,05) зниження концентрації НР у всіх зонах через кожну добу крім середньої третини тіла шлунка по малій кривизні, де відзначається тенденція до зниження концентрації НР на слизовій. На 3-ю добу прийому ІПП вірогідно найбільша концентрація НР залишається на слизовій в середній третині тіла шлунка по малій кривизні (p < 0,05). Застосування інгібіторів протонної помпи при монотерапії сприяє швидкому переходу активних форм НР-інфекції в неактивні – кокоподібні по всій слизовій шлунка. Зниження рівня НР-інфекції на слизовій шлунка відбувається за рахунок природного «змивання» бактерій при прийомі їжі і рідини в кишечник, що може сприяти формуванню фекально-орального шляху передачі.

ВЛИЯНИЕ ИНГИБИТОРОВ ПРОТОННОЙ ПОМПЫ НА ФОРМИРОВАНИЕ НЕАКТИВНЫХ (КОККООБРАЗНЫХ) ФОРМ ХЕЛИКОБАКТЕРНОЙ ИНФЕКЦИИ

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Ключевые слова: ингибиторы протонной помпы; хеликобактерная инфекция; коккообразные формы

Были комплексно обследованы 62 больных хроническим хеликобактериозом, которые накануне обследования принимали ингибиторы протонной помпы (ИПП) (длительность приёма – от 1 до 3-х суток). При тестировании после приёма ИПП в течение 1 суток НР-инфекция была выявлена в 100% случаев, однако только в неактивной коккообразной форме при высокой степени обсеменения слизистой желудка (в среднем больше (++)) при отсутствии достоверного различия (p > 0,05) данного показателя по топографическим зонам. При анализе данного показателя по одним и тем же топографическим зонам относительно длительности приёма ИПП отмечается достоверное (p < 0,05) снижение концентрации НР во всех зонах через каждые сутки кроме средней трети тела желудка по малой кривизне, где отмечается только тенденция к снижению концентрации НР на слизистой. На 3-и сутки приёма ИПП достоверно наибольшая концентрация НР остаётся на слизистой в средней трети тела желудка по малой кривизне (p < 0,05). Применение ингибиторов протонной помпы при монотерапии способствует быстрому переходу активных форм НР-инфекции в неактивные – коккообразные по всей слизистой желудка. Снижение уровня НР-инфекции на слизистой желудка происходит за счёт естественного «смывания» бактерий при приёме пищи и жидкости в кишечник, что может способствовать формированию фекально-орального пути передачи.