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Colon Motility in The Rats After Long-Term Treatment of Omeprazole and Pantoprazole.

[1]Pylypenko S.V., [1]Koval A.A., [2]Korinchak L.M., and [3]Beregova T.V.

[1]Poltava V.G. Korolenko National Pedagogical University, Poltava, Ukraine.
[2]Pavlo Tychyna Uman State Pedagogical University, Uman, Ukraine.
[3]Taras Shevchenko National University of Kyiv, Kyiv, Ukraine.

ABSTRACT

The aim of the study was to investigate the consequences of long-term use of proton pump inhibitors (PPIs) on colon motility in the rats. The study was done on 30 male albino rats which were divided into 3 groups. As a control were rats, which were injected 0.2 ml of water for 28 days intraperitoneally (i.p.). The rats of second group received omeprazole ("Sigma Aldrich", USA) and the rats of third group – pantoprazole (Ulsepan, "World Medicine", Great Britain) in dose 14 mg/kg i.p. once a day for 28 days. One day after the last administration of drugs, the spontaneous and stimulated by carbachol colon motility was recorded by the balloongraphic method. Gastrin concentration in blood serum was determined by the radioimmune method. Long-term use of omeprazole and pantoprazole leads to diminishing of spontaneous and stimulated by carbachol colon motility and increase of gastrin concentration in blood serum by 3,1-fold and 1,6-fold consequently. We concluded that suppression of colon motility after long-term use of PPIs is the result of hypergastrinemia evoked by diminishing of gastric acid secretion. The effect of omeprazole on colon motility was expressed more strongly which we associate with its greater effect on the growth of gastrin concentration.

Keywords: proton pump inhibitors, colon, motility, gastrin.

Corresponding author

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INTRODUCTION

Proton pump inhibitors (PPIs) have a leading place in the treatment of peptic ulcer disease and bleeding, Zollinger–Ellison syndrome, gastroesophageal reflux disease, Helicobacter pylori infection, Barrett esophagus, eosinophilic esophagitis, and dyspepsia [1, 2]. Also PPIs are using for prevention of gastroduodenal mucosal lesions in patients taking non-steroidal anti-inflammatory drugs (NSAIDs) or antiplatelet therapies [2]. For some of these diseases proton pump blockers are prescribed for a long time [3]. That's why long-term effects of PPIs are actively debated in the literature. The US FDA has issued a warning regarding fractures and the impaired magnesium absorption associated with the use of PPI. Thrombocytopenia, iron deficiency, vitamin B12 deficiency, rhabdomyolysis, Clostridium difficile-associated diarrhea, idiopathic thrombocytopenia and acute interstitial nephritis have also been reported with the use of PPIs [4, 5].

The least studied is the functioning of the intestinal motility after use of PPIs including long-term treatment. The data of literature about this question are limited. Kurt et al. [6] showed that omeprazole dose-dependent decreased spontaneous intestinal contractile activity when added to the organ bath in rats. Omeprazole treatment suppressed contractile activity in the distal regions of the small intestine in rats [7].

Also it is known that omeprazole reduces aboral transit of luminal contents through small bowel of mice [8].

So, the aim of this work was experimental study of spontaneous and stimulated motor activity of the colon in rats under conditions of prolonged gastric hypochlorhydria evoked by PPIs.

MATERIALS AND METHODS

Animal preparation

Thirty male Wistar albino rats each weighing approximately 160-180 g were used in this study. The study was approved by the ethics committee of the Taras Shevchenko National University of Kyiv. Animals were divided into three groups of ten in each.

As a control (the first group) were rats, which were injected 0.2 ml of water for 28 days intraperitoneally (i.p.). The second group of rats received omeprazole 14 mg/kg i.p. (manufactured by "Sigma Aldrich", USA) once a day for 28 days, which was dissolved in 0.2 ml of water for injection. Rats of the third group was injected pantoprazole (OM) at a dose of 14 mg/kg once a day i.p. for 28 days ("Ulsepan" manufactured by "World Medicine", Great Britain), dissolved in 0.2 ml of water for injection.

The study of colon motility

One day after the last administration of drugs in rats, the motor activity of the colon was recorded by the balloon graphic method [9]. The animals were taken in the test immediately after 12 hours after the last meal. Rats were narcotized with urethane (1.1 g / kg, i.p.). Into the colon of rats a latex balloon was injected, which was filled with water in a volume of 0.8 ml and attached to the automated complex "Jaguar". After 20 minutes of the equilibrium period, spontaneous motor activity of the stomach was recorded within two hours, after which a standard motility stimulator of the non-selective agonist of the acetylcholine receptors carbachol ("Sigma Aldrich", USA) in a dose of 10 μg/kg was injected i.p. Further, the recording was continued for another 2 hours, based on the duration of action of carbachol, which is 1.5-2 hours.

After the experiments conducted, the calculation and analysis of data was performed. The motor activity of the colon was characterized by a total motor index (MI) for 1 minute. The latter is calculated by the formula:

$$MI=\Sigma (hd)/T,$$

where h - the amplitude of the reductions in the milimeters of the water column (mm.w.c.), d - the length of each wave in centimeters, T - the time of the plot of the calculated curve in minutes. MI was expressed in relative units per minute (RU/min).

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After the end of experiments, the rats were killed by the introduction of a triple dose of substance for anesthesia (urethane).

Determination of the concentration of gastrin in the blood serum

Concentration of gastrin in blood serum was determined by the radioimmune method using the analytical kit of the firm "MR Biomedicals, LLC" (USA). This study was done in a day after last injection to the rats water or PPIs.

Statistical analysis

Statistical data was processed in the "Statistica 8.0" program package. To test the samples, the W Shapiro–Wilk test was used for the distribution of the investigated indicator. Since the sample checks showed a normal distribution of the studied parameters, the reliability of the data difference in the samples was estimated using Student's t-tests for independent samples. At the same time, the average value (M) and the standard error of the average (m) were calculated [10].

RESULT AND DISCUISSION

In the results of our investigations it was established that in rats of control group the frequency of spontaneous contractions in colon was 3 per minute, average amplitude of these contractions was 2,33±0,08 mm.w.c. (fig. 1A), and index of spontaneous motor activity was 678,9±10,8 RU/min (fig. 2A).

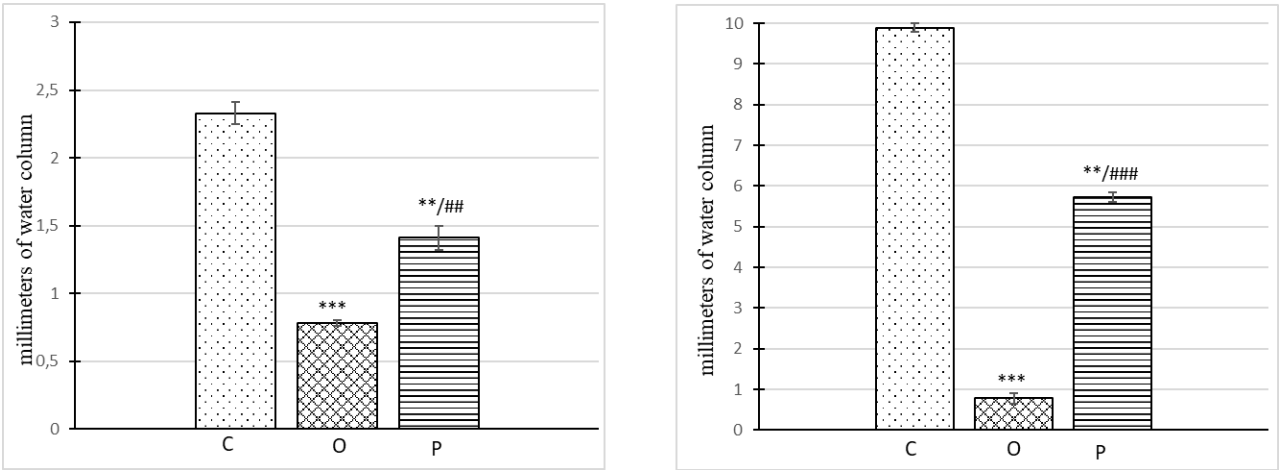

Figure 1. Amplitude of spontaneous (A) and stimulated by carbachol (B) contractions in the colon of rats after 28 days of omeprazole and pantoprazole treatment (M±m, n=10):

** - p<0,01, *** - p<0,001 – compared to the control group of animals;

- p<0,01, ### - p<0,001 – compared to the group of animals which were treated by omeprazole during 28 days.

Introduction of carbachol to the rats of control group stimulated a pronounced contractile reaction of the colon, which, on the background of unchanged frequency of contractions, was characterized by an increase in the amplitude of contractions to 9,89±0,10 mm.w.c. (fig. 1B) and the index of motor activity to 988,4±15,6 RU/min (fig. 2B).

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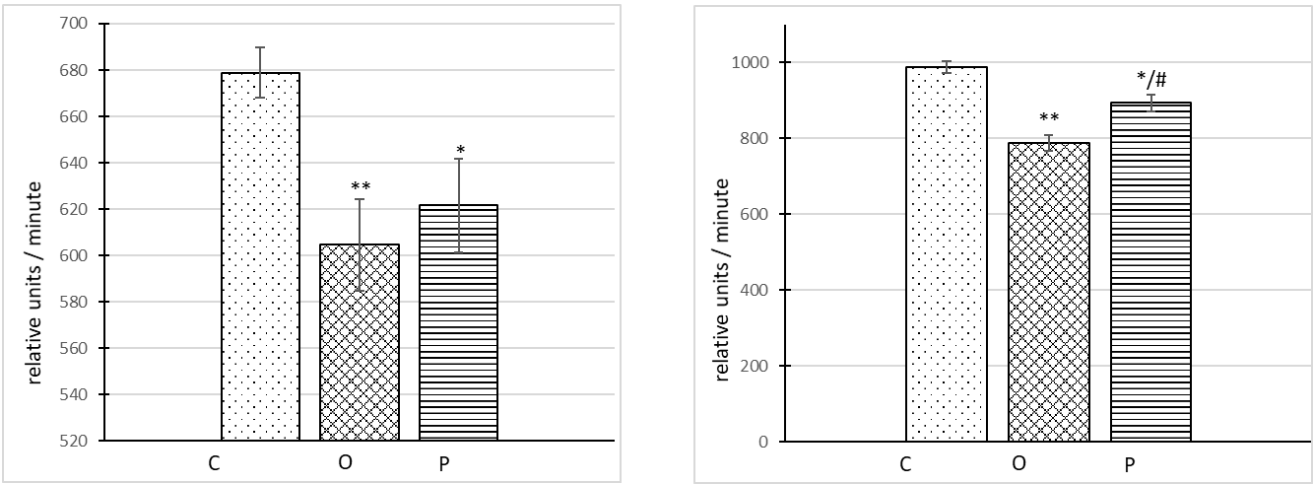

Figure 2. Index of spontaneous (A) and stimulated by carbachol (B) colon motility in rats after 28 days of omeprazole and pantoprazole treatment (M±m, n=10):

* - p<0,05, ** - p<0,01 – compared to the control group of animals;
# - p<0,05 – compared to the group of animals which were treated by omeprazole during 28 days.

In a day after 28 days of omeprazole injections the frequency of spontaneous contractions didn't change compared to the control group of animals. At this amplitude of spontaneous contractions diminished by 66,5% (p<0,001) (fig. 1A) and index of spontaneous motor activity decreased by 10,9% (p<0,01) (fig. 2A) in comparison with control.

In a group of rats who received omeprazole for 28 days, the stimulating effect of carbachol on contractile activity of the colon smooth muscles was significantly weaker compared to the control group: amplitude of contractions diminished by 80% (p<0,001) (fig. 1B), index of stimulated colon motility decreased by 20,3% (p<0,01) (fig. 2B).

Another PPI pantoprazole also influenced on spontaneous and stimulated by carbachol colon motility. In a day after last injection of pantoprazole amplitude of spontaneous contractions and index of spontaneous motor activity of colon diminished by 39,5% (p<0,01) (fig. 1A) and 8,4% (p<0,05) (fig. 2A) consequently.

After 28 days of pantoprazole treatment to the rats amplitude of contractions in the colon stimulated by carbachol decreased by 42,1% (p<0,01) (fig. 1B), index of stimulated colon motility diminished by 9,6% (p<0,05) (fig. 2B).

Thus, long-term use of PPIs omeprazole and pantoprazole leads to oppression of spontaneous and stimulated colon motility in the rats. Also, the effect of omeprazole was expressed more strongly.

The question arises about the mechanism of depressing influence of PPIs on colon motility. Analyzing the problem of colon motility under conditions of hypoacidity should also to take into account the date of literature about the influence of gastrin on the motor function of colon because the development of hyperhastrinemia against the backdrop of suppression of gastric acid secretion is an indisputable fact [11, 12]. It has been shown that the application of gastrin-17 to preparations of smooth mucus of the distal colon of guinea pigs caused relaxation of smooth muscles, which prevented the pre-introduction of the L-NAME NO synthase blocker [13]. The obtained data suggests that NO may act as a mediator of the inhibitory effect of gastrin on colon motility.

However, there are opposite data on the influence of hyperhastrinemia on motor activity of colon. Namely, it can lead to increased motility, which manifests itself in the form of diarrhea in humans [14]. Also, in patients with Zollinger-Ellison syndrome, which is a sign of high levels of gastrin in the blood, diarrhea is often observed [15, 16]. In this regard, we determined the gastrin concentration in the blood serum in rats of all groups.

It was found that after 28 days the introduction of omeprazole concentration of gastrin in serum was increased by 3.1-fold ($p<0.05$) (fig. 3), which correlates with data of other authors about the growth of the secretion of this hormone after short-term [17], and after prolonged use of proton pump inhibitors [18, 19, 20].

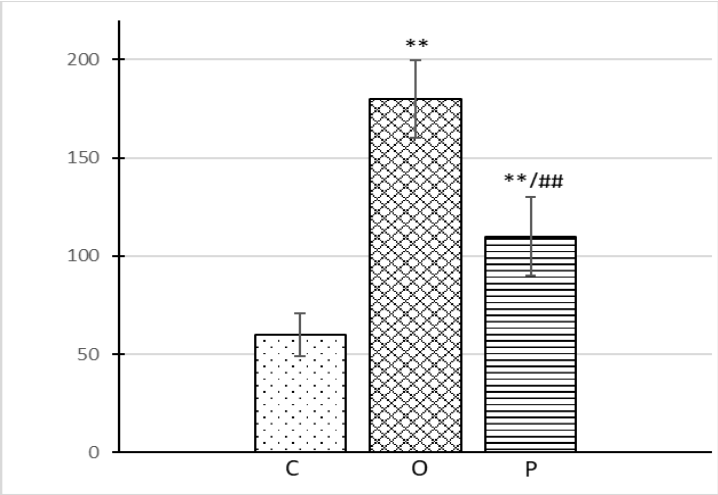

Figure 3. The concentration of gastrin in blood serum in rats of control group © and after 28 days of omeprazole (O) and pantoprazole (P) treatment (M±m, n=10):

** - $p<0,01$ – compared to the control group of animals;
- $p<0,01$ – compared to the group of animals which were treated by omeprazole during 28 days.

In a day after last injection of pantoprazole to the rats gastrin concentration in blood serum was increased by 1.6-fold ($p<0.01$) in comparison with control (fig. 3). The effect of pantoprazole on gastrin increase was weakly by 2-fold ($p<0.01$) in comparison with omeprazole (fig. 3).

We concluded that suppression of colon motility after long-term use of PPIs is the result of hypergastrinemia evoked by diminishing of gastric acid secretion. The fact that the pantoprazole is less inhibitory to colon motility is apparently due to a lower increase in the concentration of gastrin compared to omeprazole.

With regard to the diarrhea described in the literature on the background of the administration of blockers, which we have occasionally observed in rats, we believe that it has another mechanism. Formerly we have shown that after 28 days of omeprazole injection to the rats expression of CFTR channels in colon was increased and as the results secretion of water grew which may be the cause of diarrhea [21]. Thus diarrhea evoked hypergastrinemia has a hypersecretory, not hyperkinetic nature.

CONCLUSION

- Long-term use of PPIs omeprazole and pantoprazole leads to diminishing of spontaneous and stimulated colon motility in the rats.
- After 28 days of omeprazole and pantoprazole injection gastrin concentration in blood serum was increased by 3,1-fold ($p<0,01$) and 1,6-fold ($p<0,01$) consequently in comparison with control
- The effect of omeprazole on colon motility was expressed more strongly which we associate with its greater effect on the growth of gastrin concentration in blood serum in the rats.

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