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Gastric Motor Activity After Prolonged Administration Of Omeprazole And Pantoprazole.

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ABSTRACT

The aim of the study was to investigate the effects of prolonged treatment of proton pump blockers on gastric motility in the rats and compare changes with control group rats. The study of gastric motility was done on white non-linear male rats with use balloon graphic method. Farther we investigated Mg^{2+}, Ca^{2+}-ATPase and K^+(EGTA)-ATPase activity of actomyosin of smooth gastric muscles. After 28 days of administration of omeprazole and pantoprazole, the frequency of spontaneous contractions in the stomach did not change, and the amplitude of spontaneous contractions decreased by 79.7% (p <0.01) and 70.3% (p <0.01), respectively comparable to control. The index of spontaneous gastric motor activity after 28 days of omeprazole administration was 10.3% (p <0.05) lower than control. After 28 days of introduction of pantoprazole, the index of spontaneous motor activity was statistically significantly different from that of control. The amplitude of carbacholine-stimulated reductions in the stomach after 28 days of omeprazole administration was reduced by 64.5% (p <0.01), and after 28 days of pantoprazole administration, the decrease in the amplitude of stimulated contractions was statistically unreliable. The long-term administration of omeprazole significantly affected ATPase activity of actomyosin of smooth gastric muscle: Mg^{2+}, Ca^{2+}-ATPase and K^+(EGTA)-ATP activity of actomyosin of smooth gastric muscles decreased by 61% (p <0.05) and 23% (p <0.05), respectively, in comparison with control. After 28 days, the introduction of pantoprazole Mg^{2+}, Ca^{2+}-ATPase and K^+(EGTA)-ATP-ATPase activity of actomyosin of smooth stomach muscles did not significantly differ from the control (p>0,05). Long-term inhibition of gastric acid secretion by proton pump blockers leads to decrease of spontaneous and stimulated gastric motility, which manifested in the changing of functional state of the actomyosin smooth muscles of the stomach. At the same time, the effect of pantoprazole was weaker than that of omeprazole. Therefore, for long-term administration of proton pump blockers, for example, in chronic reflux esophagitis, it is advisable to appoint pantoprazole.
Keywords: gastric motility, omeprazole, pentaprazole, proton pump.

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INTRODUCTION

It is well known that the decrease of the acidity of gastric juice for any reason may lead to excessive bacterial growth in the oral cavity [1], the stomach [2, 3, 4, 5] and in the thin [6] and large intestine [2, 7] and to the development of hypergastrinemia. Both prolonged hypergastrinemia and dysbiosis can interfere with the motor-evacuation function of the digestive tract, which, in turn, will aggravate the development of chronic inflammatory process, which has a determining role in the development of tumors.

The analysis of available literature indicates the limited and contradictory data obtained by various authors regarding the motor function of the stomach under conditions of long-term hypochlorhydria. About the contradictory results in this direction is noted in the article published in the journal "Neurogastroenterology and motility" [8]. Several authors have shown that proton pump blockers lansoprazole, rabeprazole and omeprazole accelerate evacuation from the stomach of water and liquid food [9, 10, 11]. In a number of studies, the absence of an effect of secretion of hydrochloric acid (HCl) secretion on evacuation from the stomach of liquid food [8, 12, 13, 14] is shown. In the case of solid food: in some studies, the absence of the effect of HCl secretion blockers on evacuation from the stomach of solid food is shown [15, 16, 17, 18, 19, 20], in others – the inhibition of evacuation from the stomach of solid food is shown [21, 22, 23, 24, 25; 26]. Since evacuation is the result of coordinated motor activity of the stomach and duodenum, it can be concluded that the problem of the motility of the digestive tract against the background of inhibition of secretion of HCl in the stomach is not resolved.

So, the aim of the study was to investigate the effects of prolonged treatment of proton pump blockers on gastric motility in the rats and compare changes with control group rats.

METHODS

Experimental groups

The studies were conducted on 30 white non-linear male rats weighing 160-180 g, randomized to be divided into three groups of 10 animals in each. Manipulation and the keeping of animals in vivarium were carried out in accordance with international recommendations and national legislation on conducting medical-biological research [27], and they were confirmed by the conclusion of the Ethics Committee of the Taras Shevchenko National University of Kyiv. All animals received standard diet.

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 "Dr. Reddis", India) 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 20 mg/kg once a day i.p. (28 days) ("Ulsepan" manufactured by "World Medicine", Great Britain), dissolved in 0.2 ml of water for injection. Such series of experiments were repeated 3 times.

The study of gastric motility

One day after the last administration of drugs in rats, the motor activity of the stomach was recorded. 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.) (manufactured by Sigma-Aldrich Co. (St. Louis, MO, USA)).

The motor activity of the stomach was investigated by the balloon graphic method [28]. For this into the stomach of rats was injected a latex balloon, which was filled with water in a volume of 1.2 ml and attached to the automated complex "Jaguar" manufactured by PAO NPP "Saturn" (Kyiv, Ukraine). After 20 minutes of the equilibrium period, spontaneous motor activity of the stomach was recorded within an hour, after which a standard motility stimulator of the non-selective agonist of the acetylcholine receptor carbacholine (manufactured by Sigma-Aldrich Co. (St. Louis, MO, USA)) in a dose of 10 µg/kg was injected to the intravenous rats. Further, the recording was continued for another 2 hours, based on the duration of action of carbacholine, which is 1.5-2 hours.

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

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

where h is the amplitude of the reductions in mmHg, d - the length of each wave in mm., T is the time of the plot of the calculated curve. Also expected average amplitude of spontaneous and stimulated abdominal cramps in centimeters of water column.

After the experiment, the rats were killed by the introduction of a triple dose of anesthesia.

Isolation of actomyosin from the smooth muscles of the stomach

The isolation of the actomyosin from the smooth muscles of the stomach was performed according to a modified method [29], in which the use of the membrane detergent, 1% solution of the triton X-100, eliminates the impurities of mitochondrial sarcololemic and reticular- sarcololemic membranes. At the same time, the ATPase activity of myofibrils and its sensitivity to the Ca2 + ions does not change.

All manipulations were carried out at a temperature of 0-4 ºC. The stomach was removed from the stomach, and the muscular layer was homogenized. Homogenizate was suspended for 30 seconds in a solution of 40 mM KCl, 2 mM MgCl2, 0.5 mM DTT, 20 mM imidazole, pH 6.6, 0.5% Triton X-100, 0.2 mM PMSF. To collect the muscle, the suspension was centrifuged for 15 minutes at 6000 g. The residue was washed 5 times. At the first and second rinses, the Triton X-100 was injected into the solution at concentrations of 0.5% and 0.3%, respectively. As a result, the washed precipitate was used to select the actomyosin.

Actomyosin was isolated by extraction of the myosin light chain kinase complex and myosin light chain phosphatase, which included 60 mM KCl, 30 mM MgCl2, 1 mM β-mercaptoethanol, 1 mM NaN3, pH 7.6, 0.2 mM PMSF. After this, the solution was centrifuged at 10000 g for 30 minutes. Supragarden fluid contained a complex of kinase of myosin light chain and phosphatase of myosin light chain.

The resulting precipitate was resuspended in 5 mM EDTA, then centrifuged at 6000 g for 30 minutes. The sediment was left on ice for 12 hours. Then, a rough actomyosin fraction was obtained by extraction with a solution of 90 mM KCl, 2 mM EDTA, 2 mM EGRTA, 1 mM β-mercaptoethanol, 1 mM NaN3, 7.5 mM ATP, 40 mM imidazole, pH 7.2, 0.2 mM PMSF.

The supernatant formed, filtered, then was precipitated by saturation of the solution with ammonium sulfate to 60%. The precipitate was further centrifuged at 6000 g for 30 minutes. In the subsequent step, it was dissolved in a solution of composition: 60 mM KCl, 2 mM MgCl2, 1 mM NaN3, 10 mM imidazole, pH 7.0, 0.2 mM PMSF. For the removal of coarse impurities ("illumination"), the preparations of actomyosin were centrifuged at 20000 g for 30 minutes. The actomyosin solution was prepared at a concentration of 0.28 mg / ml to determine the ATPase activity of actomyosin.

ATPase activity definition

For this, the stock solution of actomyosin was diluted with a buffer solution. Since this requires an exact value of the concentration of protein in the solution, we determined it by the biuret reaction, because this technique is optimal in this range of concentrations [30].

An indicator of the physiological state of the actomyosin is Ca^{2+}, Mg^{2+}-dependent ATP-hydrolysis (adenosine triphosphatase (ATPase) activity). The ATPase activity of actomyosin was calculated from the amount of inorganic phosphate (Pi), which is formed by hydrolysis of ATP by active centers of myosin molecules, per milligram of protein per minute in an incubation medium. The number of Pi was determined using the modified Fiske-Subbauer method [31].

The ATPase reaction was carried out at 37 ºC in an incubation medium (total volume of the sample - 1.8 ml) of such composition: 2.5 mMMgCl2, 0.08 M MgCl2, 20 mM imidazole buffer, pH 7.5. To determine the

Ca^{2+}-Mg2 + -dependent ATPase activity, 0.1 mMaaCl2 was added to the incubation medium. To determine the K + (EGRTA) -ATPase activity to the incubation medium, 1 mM EGTA was added. The concentration of actomyosin in the final volume of the reaction mixture was 0.28 mg / ml. The ATPase reaction was initiated by the addition of 1 mM ATP to the protein incubation medium and stopped after 5 minutes with the addition of trichloroacetic acid. The ATPase activity of actomyosin was expressed in nmol Pi/min per 1 mg of protein.

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 [32].

RESULTS

As a result of the studies, it was shown that after 28 days of administration of omeprazole and pantoprazole, the frequency of spontaneous contractions in the stomach did not change (Fig. 1B, 1C). At the same time, the amplitude of spontaneous contractions decreased by 79.7% (p<0.01) and 70.3% (p<0.01), respectively, compared with control. Although the difference between the effects of omeprazole and pantoprazole after 28 days of administration was insignificant (9.4%), it was statistically significant (p<0.05). The index of spontaneous motor activity of the stomach after 28 days of omeprazole administration was 10.3% (p<0.05) lower than control. After 28 days of introduction of pantoprazole, the index of spontaneous motor activity was statistically significantly different from that of control.
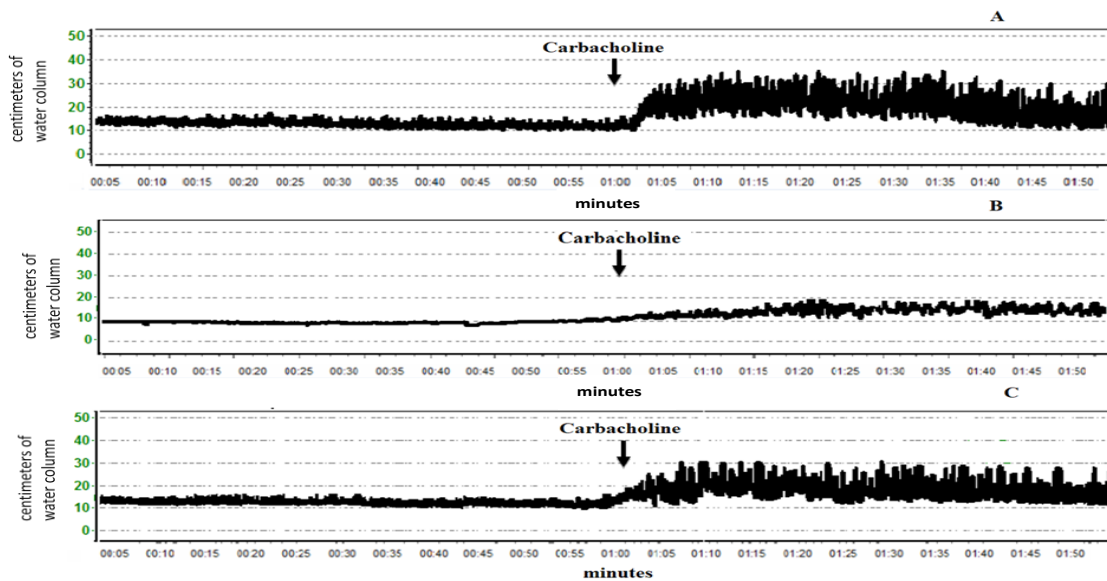

Figure 1. Original records of spontaneous and stimulated gastric motility in rats:

A – gastric motility in the rat of the control group;
B – gastric motility after 28 days of administration of omeprazole;
C – gastric motility after 28 days of administration of pantoprazole.
The arrow shows the time of the introduction of carbacholine.

That is the negative effect of pantoprazole on the index of stimulated stomach motility was 1.9 times (p <0.05) weaker than the effect of omeprazole.

More pronounced was the effect of proton pump blockers on motor activity of the stomach, stimulated by carbacholine. The amplitude of carbacholine stimulated contractions in the stomach after 28

days of omeprazole administration decreased by 64.5% (p<0.01), and after 28 days of administration of pantoprazole – by 36.9% (p>0.05). Thus, the effect of pantoprazole on the amplitude of stimulated contractions in the stomach was 1.75 times (p <0.05) weaker than that of omeprazole. Under the influence of omeprazole and pantoprazole, the index of spontaneous motor activity of the stomach stimulated by carbacholine was reduced by 36.8% (p <0.05) and 19.8% (p<0.05), respectively.

The long-term administration of omeprazole significantly affected ATPase activity of actomyosin of smooth gastric muscles: Mg^{2+}, $Ca2^{+}$-ATPase and K^{+} (EGTA)-ATPase activity of actomyosin of smooth gastric muscles decreased by 61% (p<0.05) and 23% (p<0.05), respectively, in comparison with control. After 28 days, the introduction of pantoprazole $Mg2 +$, $Ca2 + $ - ATPase and $K +$ (EGTA)-ATPase activity of actomyosin of smooth gastric muscles was diminished by 33% (p<0.05) and 11% (p>0,05) in comparison with control (Figures 2, 3).
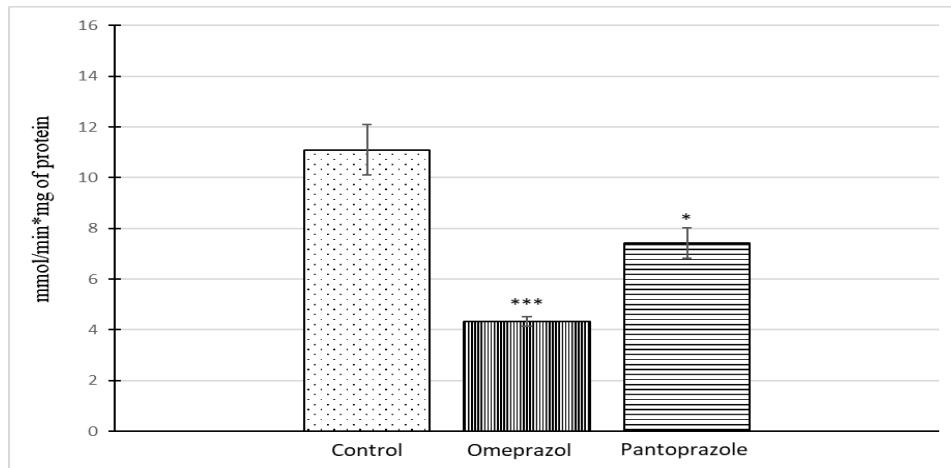

Figure 2. Mg2 +, Ca2 + - ATPase actomyosin activity of gastric smooth muscle in rats, (M $\pm$ m):

Control – control group of rats (n = 10),
O – group of rats after 28 days of administration of omeprazole (n = 10),
P – group of rats after 28 days of administration of pantoprazole (n = 10)
 * - p <0,05, *** - p <0,001 compared with the control.

Figure 3. K+ - ATPase actomyosin activity of gastric smooth muscle in rats, (M $\pm$ m):

Control – control group of rats (n = 10),
O – group of rats after 28 days of administration of omeprazole (n = 10),
P – group of rats after 28 days of administration of pantoprazole (n = 10)
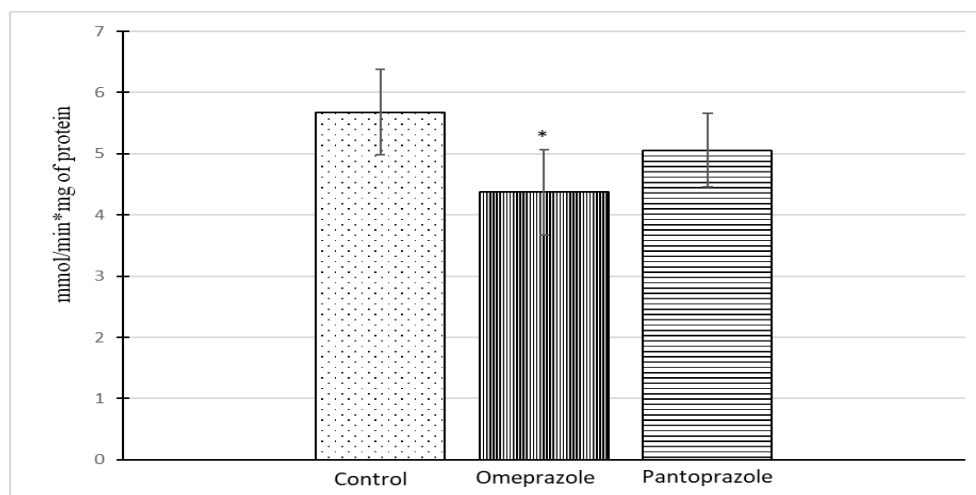 * - p <0,05, *** - p <0,001 compared with the control.

DISCUSSION

Gastroesophageal reflux disease is a common disease attended by the gastroenterologist. A systematic review found a prevalence of GERD of 10% to 20% in the Western World (Western Europe and North America) with a lower prevalence in Asia [33]. The proton pump inhibitors are the first choice drugs and the most commonly medication used for the treatment of gastroesophageal reflux disease. Inhibitors are prescribed from 4 to 6 weeks. That's why the investigation of influence of the proton pump inhibitors on the gastro-intestinal motility is necessary. Especially, if to take into account the data about the diminishing of evacuation from the stomach after long-term use of omeprazole [24]. As the data about influence of the proton pump inhibitors on gastric motility are limited we decided to investigate gastric motility in rats after long-term treatment omeprazole and pantoprazole.

In our experiments, only males were used because the duration of the experiment was 28 days. Every day we took animals by hand and injected substances. Female rats, unlike male rats, behaved aggressively. Female rats are more stressful. This corresponds to the literature data about sex differences in rats [34]. The effect of stress on the morphofunctional state of the gastrointestinal tract was very good studied. Our results have some limitations which are connected with sex differences in rats. But in the future we plan to conduct similar studies in female rats.

We established that in rats after 28 days injection of omeprazole gastric motility was suppressed. These results are in agreement with the data of other authors, which showed that the inhibition of HCl secretion in humans by therapeutic doses of omeprazole (20 mg daily for 7 days) led to suppression of evacuation from the stomach of solid food against the background of increased contractions in the antrum and no changes in the duodenal motility [24]. Given that the fact that the evacuation function is a reflection of motility, analyzing this work, we made the conclusion that the motility of the fundus of the stomach in humans after 7 days of administration of omeprazole is suppressed. The weaker effect of pantoprazole on gastric motility is apparently the result of a weaker inhibition of gastric secretion than after the administration of omeprazole.

We hypothesized that the cause of disturbance of the motility of the digestive tract in conditions of prolonged hypochlorhydria is the development of inflammatory process in the stomach and intestine, which causes dysbiosis and hypergastrinemia. In turn, disturbance of the motility of the digestive tract promotes the colonization of the stomach by intestinal microflora. At first, excessive bacterial growth in the small intestine develops, where bacteria from the colon can easily migrate. Pyloric sphincter, it would seem, should have prevented the ingestion of intestinal bacteria into the stomach. However, due to the duodeno-gastric reflux, the microorganisms enter the stomach. Duodeno-gastric reflux is one of the components of the functioning of the motor activity of the digestive tract. Under normal conditions, the contents of the duodenum, which due to reflux enters the stomach, is delayed in it for a short time. However, in the case of suppression of the stomach motility, which arose after prolonged administration of omeprazole, the intestinal contents in the stomach was delayed for a long time, which contributed to the adhesion of microorganisms that inhabit the colon, to the mucous-epithelial layer. Suppressed gastric motility contributed to delay in the gastric transient microflora.

One of the main causes of gastrointestinal disorders is a change in the motor function of the gastrointestinal tract, which is based on violations of smooth muscle contraction [35, 36, 37]. Changes in the contractile activity of the smooth muscles of the gastrointestinal tract, in particular the stomach of rats, is associated with a violation of the interaction of contractile proteins within the functional complexes that provide a reduction process at the molecular level [38]. ATPase activity is one of the main functional characteristics of the complex of contiguous proteins – actomyosin. Therefore, in the following series of studies, we studied the functional state of the actomyosin smooth muscles of the stomach under the conditions of long-term administration of omeprazole and pantoprazole.

Mg^{2+}, Ca^{2+} -ATPase activity is manifested in the presence of Mg^{2+} and Ca^{2+} ions that are necessary for muscle contraction [39]. In the absence of dual cations, which is achieved by addition in the environment of EGTA, actomyosin ATPase is activated by monovalent cations. Such the activity of actomyosin is called K^+ (EGTA)-ATPase activity. It is believed that ions K^+, NH_4^+, Rb^+, in contrast to dual valent cations of

calcium and magnesium, reduce the ability of myosin to bind ATP. Some authors talk about it as a relaxing ATPase activity [29].

The reduction of muscles is due to the cyclic interaction of the head of myosin with actin accompanied by the process of hydrolysis of ATP in the active center of myosin. As a result of the release of energy during the hydrolysis of ATP, the movement of actin and myosin filaments occurs in relation to each other. The regulation of this process is quite complex and multicomponent, includes such components of signaling systems as calcium, calmodulin, calmodulin kinase, myosin light chain kinase [40, 41, 42, 43].

Since the change in calcium concentration is the trigger stage of this complex process, the disturbance of calcium homeostasis can not but be reflected in the process of contraction and its main mechanism – ATPase activity. Proton pump inhibitors are used for therapeutic purposes for the treatment of acid-dependent diseases of the gastrointestinal tract. The short-term intake of proton pump inhibitors does not affect the absorption of Ca^{2+} and Mg^{2+} in the intestine, but prolonged use leads to hypocalcemia and hypomagnesaemia [44, 45, 46, 47, 48, 49, 50]. Violations of calcium homeostasis under the influence of OM can be explained by dysfunction of calcium-sensitive receptor (CaR) – the main sensor of extracellular Ca^{2+} and calcium homeostasis regulator. The activity of CaR is abolutely regulated by amino acids and pH [51]. In addition, CaR is involved in the regulation of a number of other processes, in particular, the release of gastrin by G-cells, secretion of HCl by parietal cells of the stomach, secretion and proliferation of the epithelial cells of the gastrointestinal tract, the processes of water transport through the epithelium of the colon and differentiation [52]. Therefore, the decrease in the ATPase activity of the complex of actomyosin concomitant proteins of the smooth muscles of the stomach can be explained by a decrease in intracellular Ca^{2+} concentration due to CaR dysfunction, which occurs when the secretion of acid under the influence of omeprazole and pantoprazole is reduced. Consequently, the decrease in the ATPase activity of actomyosin under the influence of omeprazole and pantoprazole may be explained by the complex effect of the drug on the transport of Ca^{2+} and Mg^{2+} cations, which occurs due to changes in the secretion of HCl in the stomach.

CONCLUSIONS

Long-term inhibition of gastric acid secretion by proton pump blockers leads to decrease of spontaneous and stimulated gastric motility, which manifested in the changing of functional state of the actomyosin smooth muscles of the stomach. At the same time, the effect of pantoprazole was weaker than that of omeprazole. Therefore, for long-term administration of proton pump blockers, for example, in chronic reflux esophagitis, it is advisable to appoint pantoprazole.

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Competing interests

The authors declare that there is no conflict of interests.

Authors' contributions

Experimental work on determining the motor activity of the stomach under conditions of administration of omeprazole and pantoprazole has been carried out, Mg^{2+}, Ca^{2+} and K^+ - ATPase actomyosin activity of gastric smooth muscle in rats was analised by all autors. Search for literature sources – Korinchak L.M., Pylypenko S.V. Statistical processing of results and their analysis – Koval A.A., Pylypenko S.V. Preparation of materials for printing – Pylypenko S.V. Experiment planning – Pylypenko S.V.

Ethics approval and consent to participate

Institutional ethical clearance for publication.

List of abbreviation

ATPase: adenosinetriphosphatase
CaR: calcium-sensitive receptor
HCl: hydrochloric acid
Pi: inorganic phosphate

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