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STUDY OF ANTISECRETORY ACTIVITY OF DINITRATE 2-PHENYL-9-DIETHYLAMINOETHYLIMIDAZO[1,2-A] BENZIMIDAZOLE BY METHOD OF CONTINUOUS PERFUSION OF RATS' STOMACHS

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Nowadays, effective pharmacotherapy of acid-dependent gastrointestinal diseases remains an urgent problem of modern gastroenterology. In this regard, the search for new drugs with a pronounced antisecretory activity still continues; their aim is to keep the control over the acid production safe and effective.

The aim of this study was an experimental study of the antisecretory activity of the substance and the finished dosage form (FDF) of dinitrate 2-phenyl-9-diethylaminoethylimidazo[1,2-a]benzimidazole.

Materials and Methods. The study of antisecretory activity was performed by method of a continuous perfusion of rats' stomachs. The studied substance was administered at the doses of 3, 10 and 30 mg/kg, and the FDF – at the doses of 13 and 26 mg/kg. The substance of Ranitidine (Sigma Aldrich, USA) was used as a reference object in the study of the antisecretory activity of the substance under study, and Ranitidine (Hemofarm A.D., Serbia) was used as a reference drug in the study of the FDF. In order to determine the stimulated secretion immediately before collecting the samples of the perfusate, histamine was administered subcutaneously at the dose of 5 mg/kg. The content of hydrochloric acid in the perfusate was determined by titration of a 0.01 M sodium hydroxide solution. The acidity value was determined in terms of the debit-hour of hydrochloric acid.

Results and discussion. The obtained experimental data showed that the studied substance at the dose of 30 mg/kg decreased the basal hydrochloric acid secretion by 54%, which significantly exceeded the antisecretory effect of Ranitidine by 1.8 times. The FDF at the dose of 26 mg/kg, statistically reliable relative to the control and the group treated with Ranitidine, decreased the basal secretion of gastric juice by 33%. The substance at the dose of 30 mg/kg reliably suppressed the stimulated secretion of hydrochloric acid by 80%, while Ranitidine did it by 56%. The FDF at the dose of 26 mg/kg decreased the histamine-stimulated secretion by 66%, and Ranitidine did it by 52%, which was statistically reliable.

Conclusions. The studied substance and its dosage form are more effective in suppressing basal activities and exceed the anisecretory activity of H_2-histamine antagonists of Ranitidine under the conditions of the secretion stimulated by histamine.

Keywords: dinitrate 2-phenyl-9-diethylaminoethylimidazo[1,2-a]benzimidazole, antisecretory effect, basal secretion, stimulated secretion, preclinical studies

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ИЗУЧЕНИЕ АНТИСЕКРЕТОРНОЙ АКТИВНОСТИ ДИНИТРАТА 2-ФЕНИЛ-9-ДИЭТИЛАМИНОЭТИЛИМИДАЗО[1,2-А] БЕНЗИМИДАЗОЛА МЕТОДОМ НЕПРЕРЫВНОЙ ПЕРФУЗИИ ЖЕЛУДКА КРЫС

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Эффективная фармакотерапия кислотозависимых заболеваний ЖКТ на сегодняшний день остается актуальной проблемой современной гастроэнтерологии. В связи с этим, продолжается поиск новых лекарственных препаратов, обладающих выраженной антисекреторной активностью, с целью безопасного и эффективного контроля кислотопродукции.

Целью данного исследования – экспериментальное изучение антисекреторной активности субстанции и готовой лекарственной формы (ГЛФ) динитрата 2-фенил-9-диэтиламиноэтилимидазо[1,2-а]бензимидазола.

Материалы и методы. Исследование антисекреторной активности выполняли методом непрерывной перфузии желудка крыс. Изучаемая субстанция вводилась в дозах 3, 10 и 30 мг/кг, а ГЛФ в дозах 13 и 26 мг/кг. В качестве объекта сравнения при исследовании антисекреторной активности субстанции исследуемого вещества была использована субстанция ранитидина (Sigma Aldrich, США), а в качестве препарата сравнения при изучении ГЛФ – Ранитидин (Хемофарм А.Д., Сербия). С целью определения стимулированной секреции непосредственно перед началом сбора образцов перфузата подкожно вводился гистамин в дозе 5 мг/кг. Содержание соляной кислоты в перфузате определялось титрованием 0,01М раствором натрия гидроксида. Величину кислотности определяли в пересчете на дебит-час соляной кислоты.

Результаты. Полученные экспериментальные данные показали, что изучаемая субстанция в дозе 30 мг/кг снижала базальную секрецию соляной кислоты на 54%, что достоверно превышало антисекреторное действие ранитидина в 1,8 раз. ГЛФ в дозе 26 мг/кг, достоверно относительно контроля и группы, получавшей ранитидин, снижала базальную секрецию желудочного сока на 33%. Субстанция в дозе 30 мг/кг достоверно подавляла стимулированную секрецию соляной кислоты на 80%, в то время как ранитидин на 56%. ГЛФ в дозе 26 мг/кг снижала стимулированную гистамином секрецию на 66%, а ранитидин на 52%, что статистически достоверно.

Заключение. Изучаемые субстанция и ГЛФ более эффективно подавляют базальную и превосходят антисекреторную активность H_2-гистаминоблокатора ранитидина в условиях стимулированной гистамином секреции.

Ключевые слова: 2-фенил-9-диэтиламиноэтилимидазо[1,2-а]бензимидазол, антисекреторное действие, базальная секреция, стимулированная секреция, доклинические исследования

INTRODUCTION

Nowadays, the treatment of acid-dependent diseases, such as a gastroesophageal reflux disease (GERD), gastric and duodenal kinds of ulcer, functional dyspepsia, appears to be an urgent problem in modern clinical gastroenterology [1–4]. In the treatment of acid-dependent diseases, the main pathogenetic principle is the suppression of the secretion of hydrochloric acid by parietal cells of the gastric mucosa, which eliminates or attenuates the main clinical manifestations of the above mentioned diseases [5, 6].

The inhibition of HCl secretion also significantly eliminates the manifestations of gastrointestinal complications when non-steroidal anti-inflammatory drugs (NSAIDs), antiaggregants and anticoagulants are taken. In the cases of infection with Helicobacter pilory, the inhibition of HCl secretion increases the effectiveness of the eradication therapy by increasing the anti-Helicobacter activity of antibacterial drugs [7, 8].

Hydrogen-potassium adenosine triphosphatase blockers (proton pump inhibitors), histamine H2 receptor antagonists, selective M-cholinoblockers, antacids, and partly gastrin and cholecystokinin CCK-2 receptor blockers are used as antisecretory agents [2, 4, 5, 9].

Of course, the positive effects of the drugs of these groups are undeniable and all of them are widely used in the treatment of acid-dependent diseases, but they have certain disadvantages and side effects.

Before the introduction of proton pump inhibitors into the clinical practice, H2-histamine receptor antagonists were “the gold standard” of the antisecretory therapy [9]. However, along with the resistance to their

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use in about 1/5 patients with acid-dependent diseases, there is a rapid development of tolerance in previously susceptible patients, withdrawal syndrome. In addition, the side effects characteristic of this group of drugs, such as decreased libido, bradycardia, hepatotoxicity and others, largely limit the intake and prescription of these preparations [10–14].

It has been proved that a long-term treatment with proton pump inhibitors can cause a number of undesirable effects, such as magnesium deficiency, hypergastrinemia and a risk of tumors, vitamin B12 deficiency, acute interstitial nephritis, osteoporosis and an increased risk of fractures, an intestinal bacterial overgrowth syndrome, a risk of cardiovascular accidents [15].

M-cholinoblockers, including selective ones, such as pyrenzepine, have a full range of side effects, characteristic of the "classic" non-selective drugs, although less pronounced, such as dry mucous membranes, tachycardia, accommodation disorders and photophobia, intestinal and bladder atony, dizziness, headaches [11, 16–18].

Under modern conditions, antacid agents can be considered only as additional means of auxiliary therapy of acid-dependent diseases [11].

In this regard, it remains relevant to search for new acid-dependent diseases treatment. They should be safer, more effective in suppressing acidity and, at the same time, available to the consumer.

Currently, the pharmaceutical market offers a wide range of drugs based on benzimidazole derivatives, such as anti-ulcer agents, inhibitors of hydrogen-potassium adenosine triphosphatase – omeprazole, lansoprazole; antihistamines – astemizole; antihypertensive agents – telmisartan, candesartan; antiviral agents – enviradin, maribavir; antiparasitic agents – albendazole, oxfendazole and many others[19–22]. This factor indicates a significant medical value of this group of chemicals and provides a high interest in them.

The aim of this study was the experimental study of the antisecretory activity of the substances and the finished dosage forms of dinitrate 2-phenyl-9-diethylaminoethylimidazo[1,2-a]benzimidazole by the method of a continuous perfusion of the rats' stomachs.

MATERIALS AND METHODS

Animals

The studies of the antisecretory activity were performed on outbred Wistar rats of both sexes (aged 10–12 weeks) weighing 180.0–250.0 grams. The variation in the initial mass of the animals in the group did not exceed 10% [23]. The animals were received from "Rappolovo", the Federal State Unitary Enterprise "Nursery of laboratory animals".

The conditions of keeping the animals met the requirements of the Decree of the Chief State Sanitary Doctor of the Russian Federation No.51 dated 29.08.2014 "On approval of SP 2.2.1.3218-14 "Sanitary and epidemiological requirements for the device, equipment and maintenance of experimental biological clinics (vivaria)".

During the experiment, the animals were kept under controlled conditions: the ambient temperature of 20-26°C and the relative humidity of 30–70%. Macrolon cells T-3 (for rats) equipped with steel grating covers were used to accommodate the animals. Sawdust was used as a nesting material. The animals were on a standard diet with a free access to feed (Complete feed recipe PK-120 for the maintenance of laboratory animals, GOST R 50258-92, the manufacturer of "Laboratory Feed"), and water. A nesting material, cages and accessories, drinking bowls changed weekly.

Manipulations with the experimental animals were performed in accordance with the generally accepted ethical standards adopted by the European Convention for the protection of vertebrate animals used for experimental and other scientific purposes (1986) and taking into account the International recommendations of the European Convention for the protection of vertebrate animals used in experimental studies (1997) [24, 25].

Investigated substances

The studied pharmaceutical substance of dinitrate 2-phenyl-9-diethylaminoethylimidazo[1,2-a]benzimidazole is a fine crystalline powder of a white or light gray color. It is moderately soluble in water. For the studies, purified water was used as a solvent of the substance during intragastric administration.

The finished dosage form of dinitrate 2-phenyl-9-diethylaminoethylimidazo[1,2-a]benzimidazole was presented as film-coated tablets: 60 mg, biconvex, light green, odour-free.

For the research, a weighed portion of the finished dosage form or reference preparations, previously ground into powder, was taken and dissolved in purified water. The resulting suspension was administered intragastrically using an atraumatic gastric catheter. The maximum volume for intragastric administration to rats did not exceed 3.0 ml for the animals weighing up to 200 g, 5.0 ml for the animals from 200 to 240 g, and 6.0 ml for the animals weighing more than 240 g.

Reference preparations

In the experiments on the study of basal and stimulated secretion of a pharmaceutical substance, Ranitidine (Sigma Aldrich, USA) was chosen as the reference preparation. In the study of the antisecretory action of the finished dosage form, Ranitidine was used (Hemofarm A.D., Serbia, series M703084).

Study design

In the first series of the experiments, the influence of the studied substance at the doses of 3 mg/kg, 10 mg/

kg and 30 mg/kg on the basal and histamine-stimulated secretion of hydrochloric acid was evaluated. The substance of Ranitidine at the doses of 3 mg/kg, 10 mg/kg and 30 mg/kg (Sigma Aldrich, USA) was used as the reference object. The data obtained were used to calculate the ED50 value for the substance of dinitrate 2-phenyl-9-diethylaminoethylimidazo[1,2-a]benzimidazole. Further on, in the study of the antisecretory activity, the doses of the finished dosage form (FDF) equal to the ED50 values were used, and the doses of the reference drug were calculated relative to the therapeutic dose for a person, taking into account the interspecific transfer coefficient; it amounted to 28 mg/kg. The control group of the animals received a solvent (purified water) in the equivolume amount of the administered drugs.

Before the experiment, the animals were subjected to a 24-hour food deprivation with a free access to water. After the anesthesia with chloral hydrate (350 mg/kg), a median laparotomy was performed. The stomach was removed to the surgical wound. A cannula was inserted through the discission in the proximal part of the duodenum up to the level of the pyloric sphincter. It was fixed with a ligature. The second cannula was inserted into the lumen of the stomach through the discission in the cardiac part and then fixed to the lower food sphincter. The stomach was perfused through the esophageal cannula with a 0.1 M phosphate buffer solution (pH 7.4, the temperature 37°C, 77.4 ml of 1M disodium hydrogen phosphate and 22.6 ml of 1M sodium dihydrogen phosphate per 100 ml of buffer) using a peristaltic pump at the constant speed of 0.5 ml/min. The perfusion samples were collected from the pyloric cannula.

In order to study basal secretion, 3 samples of the perfusate were collected at a 20-minute interval for 1 hour. The test substance was injected intragastrically through the gastric catheter 1 hour before the beginning of the sample collection. The finished dosage form (FDF) was administered intragastrically through the gastric catheter 2 hours before the beginning of the sample collection.

The acid content in the perfusate was determined by titration with a 0.01 M sodium hydroxide solution. The acidity value was determined in terms of the debit-hour of hydrochloric acid.

In order to determine the stimulated secretion, immediately before the collection of the perfusate samples, histamine dihydrochloride was administered subcutaneously at the dose of 5 mg/kg. The subcutaneous administration was carried out with sterile syringes. The test substance was administered 1 hour before the collection of perfusate samples intragastrically through the gastric catheter.

The acid content in the perfusate was determined by titration with a 0.01 M sodium hydroxide solution. The acidity value was determined in terms of the debit-hour of hydrochloric acid.

The calculation of the debit-hour of hydrochloric acid:

Dh = V1*E1*0,001+V2*E2*0,001+V3*E3*0,001,

where Dh is the debit-hour of hydrochloric acid, mmol; V is the volume of the portion of the gastric contents, ml; E is the concentration of free hydrochloric acid of the same portion in the titration units; 0.001 is the amount of hydrochloric acid in 1 ml of the gastric contents at the concentration of 1 mmol/l.

Determined indicators

To evaluate the antisecretory effect, the content of hydrochloric acid in the gastric juice was determined under the conditions of basal and histamine-stimulated secretion (total acidity), and the debit-hour of hydrochloric acid was calculated. According to the results of the study, the ED50 values were calculated for the studied substance, the finished dosage form and Ranitidine.

Statistical processing

The obtained experimental data were analyzed using the method of variation statistics. The summary tables show the group averages (M) and the standard error of the mean (m). The intergroup differences were analyzed using a nonparametric test – Mann-Whitney U-test. The differences were determined at a 0.05 significance level. For statistical processing of the results, the "StatPlus 2009" software package was used.

RESULTS

The analysis of the experimental data showed that the test substance at the dose of 10 mg/kg and 30 mg/kg statistically reliably decreased the basal hydrochloric acid secretion relative to the control by 35% and 54%, respectively. The administration of the substance at the dose of 3 mg/kg did not significantly affect the basal secretion of hydrochloric acid. Ranitidine, at the doses similar to the studied substance, also contributed to the suppression of the secretion statistically reliably by 22% and 29% relative to the control, respectively. Hereby, the substance of the test drug at the dose of 30 mg/kg decreased the basal secretion relative to Ranitidine significantly more effectively (Table 1).

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Table 1 – Influence of the pharmaceutical substance of dinitrate 2-phenyl-9-diethylaminoethylimidazo[1,2-a]benzimidazole on basal gastric secretion

Substance	Dose	Debit-hour of hydrochloric acid mg-EQ/hour	Percentage of secretion suppression (%)
Control Purified water	–	0.27±0.010	–
Test substance	3 mg/kg	0.22±0.023	–18
Test substance	10 mg/kg	0.18±0.004*	–35
Test substance	30 mg/kg	0.13±0.009*#	–54
Ranitidine	3 mg/kg	0.26±0.017	–4
Ranitidine	10 mg/kg	0.21±0.014*	–22
Ranitidine	30 mg/kg	0.19±0.007*	–29

*Note: * – reliability relative to control P<0.05*
 # – reliability compared to the group treated with Ranitidine, P<0.05

The data reflecting the percentage of the decreased basal secretion relative to the control, made it possible for us to calculate the ED50 values for the test substance and Ranitidine (Fig. 1, 2). The calculated data were 26 mg/kg for the test substance, and 54.0 mg/kg for Ranitidine.

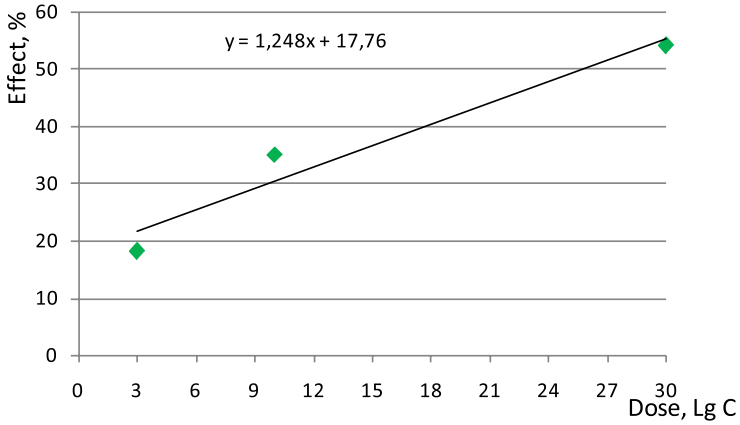

Figure 1 – Calculation of the ED50 value of basal secretion suppression of hydrochloric acid by the substance of dinitrate 2-phenyl-9-diethylaminoethylimidazo[1,2-a]benzimidazole

The finished dosage form at the dose of 26 mg/kg contributed to a decrease in the basal level of the secretion reliably relative to the control by 33%. The results obtained are statistically reliable relative to the control and the values of the group treated with Ranitidine at the dose of 28 mg/kg (Table 2).

Table 2 – Influence of the finished dosage form of dinitrate 2-phenyl-9-diethylaminoethylimidazo[1,2-a] benzimidazole on basal gastric secretion

Substance	Dose	Debit-hour of hydrochloric acid, mg-Eq/hour	Percentage of secretion suppression (%)
Control Purified water	–	0.259±0.005	-
Finished dosage form	26 mg/kg	0.172±0.004*#	–33
Ranitidine	28 mg/kg	0.207±0.007*	–20

*Note: * – statistical reliability relative to control P <0.05*
 # – statistical reliability relative to the group treated with Ranitidine P <0.05

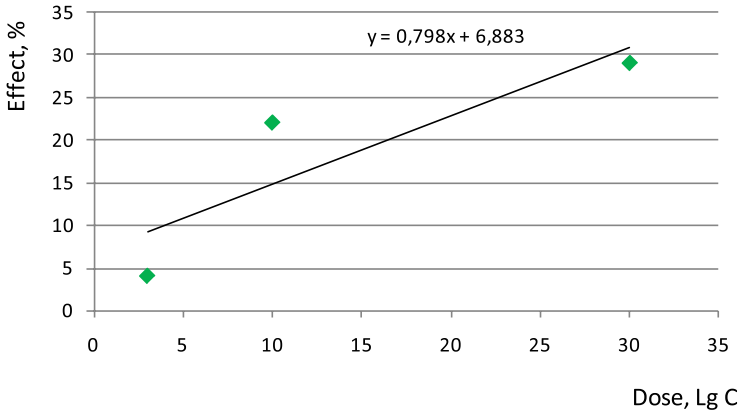

Figure 2 – Calculation of the ED50 value of basal secretion suppression of hydrochloric acid by the substance of Ranitidine

According to the results of the study stimulated by histamine secretion, it was established that the administration of histamine, increased the production of hydrochloric acid by 1.8 times relative to the basal level. The studied substance significantly inhibited the secretion of hydrochloric acid at all the studied doses. At the dose of 30 mg/kg, the secretion decreased by 80%, while Ranitidine inhibited the secretion by 56%, which is statistically reliable. The studied substance and Ranitidine at the dose of 10 mg/kg also contributed to a statistically reliable suppression of the acid production relative to the control, but no statistically reliable intergroup differences were observed. The administration of the dose of 3 mg/kg did not have the expected pharmacological effect either in the experimental group or in the reference group (Table 3).

Table 3 – Influence of the pharmaceutical substance of dinitrate 2-phenyl-9-diethylaminoethylimidazo[1,2-a]benzimidazole on histamine-stimulated gastric secretion

Substance	Dose	Debit-hour of hydrochloric acid mg-Eq/hour	Percentage of secretion suppression (%)
Control	–	0.51±0.022	–
Test substance	3 mg/kg	0.40±0.015*	–22
Test substance	10 mg/kg	0.23±0.011*	–56
Test substance	30 mg/kg	0.10±0.008*#	–80
Ranitidine	3 mg/kg	0.46±0.032	–10
Ranitidine	10 mg/kg	0.29±0.013*	–43
Ranitidine	30 mg/kg	0.22±0.013*	–56

*Note: * – statistical reliability relative to control P <0.05*
 # – statistical reliability relative to the group treated with Ranitidine P <0.05

The value of ED50 was calculated by the trend equation; for the substance under study it was 13.0 mg/kg (Fig. 3); for Ranitidine it was 23.6 mg/kg (Fig. 4).

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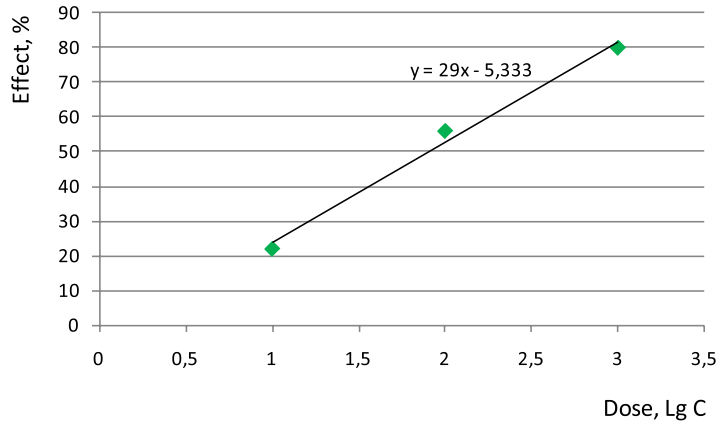

Figure 3 – Calculation of the ED50 value for the substance of dinitrate 2-phenyl-9-diethylaminoethylimidazo[1,2-a]benzimidazole under the conditions of histamine-stimulated secretion

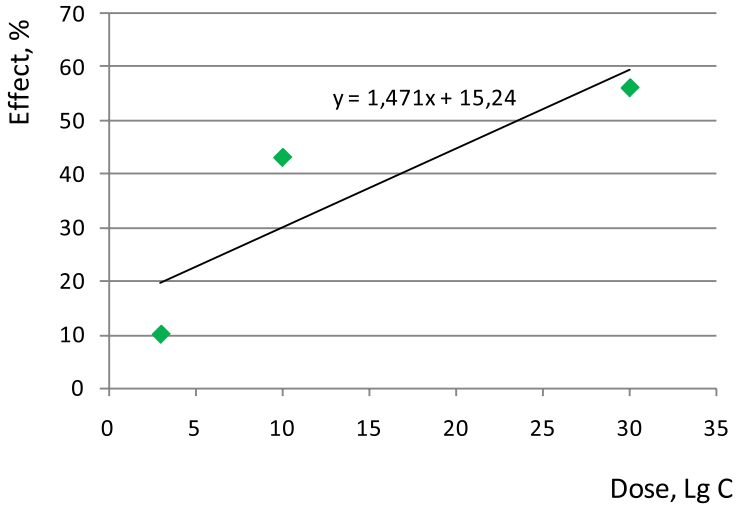

Figure 4 – Calculation of the ED50 value for the substance of Ranitidine under the conditions of histamine-stimulated secretion

According to the results of the study of histamine-stimulated secretion, it was established that the FDF of dinitrate 2-phenyl-9-diethylaminoethylimidazo [1,2-a]benzimidazole at the dose of 26 mg/kg statistically reliably inhibited hydrochloric acid secretion by 66%, while Ranitidine did it by 52% (Table 4).

Table 4 – Influence of the finished dosage form of dinitrate 2-phenyl-9-diethylaminoethylimidazo[1,2-a] benzimidazole on histamine-stimulated gastric secretion

Substance	Dose	Debit-hour of hydrochloric acid mg-Eq/hour	Percentage of secretion suppression (%)
Control	–	0.522±0.010	–
FDF	13 mg/kg	0.179±0.008*#	–66
Ranitidine	28 mg/kg	0.250±0.008*	–52

Note: * – statistical reliability relative to control P <0.05
– statistical reliability relative to the group treated with Ranitidine P <0.05

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AUTHOR CONTRIBUTIONS

All authors had equally contributed to the research work.

CONFLICTS OF INTEREST

The authors and peer reviewers of this paper report no conflicts of interest.

DISCUSSION

Benzimidazole contains nitrogen atoms of two types (pyrrole and pyridine) both acting as a donor and a proton acceptor, and existing in two tautomeric forms. Benzimidazole Bicycle can not only attach or give a proton, but also easily enter into various non-valent interactions (hydrogen bonds, van der Waals interactions, stacking interactions). These features of the structure of the benzimidazole molecule cause the possibility of its binding to a variety of therapeutic targets, providing a wide range of biological activity of benzimidazole derivatives.

The spectrum of benzimidazole derivatives' biological activity includes antiviral [26], antifungal [27], antimicrobial [28], anticancer [29], anthelmintic [30], analgesic and antipyretic [31], antidiabetic [32], antiprotozoal [33], antioxidant [33, 34], anticonvulsant [27], antipsychotic [35], antiulcer [36], anesthetic [37] and other types of activity.

A significant medical value of benzimidazole-containing drugs provides a high interest and an intensive development of this direction in pharmacology.

The analysis of the data obtained during the experiment revealed the capability of the studied substance of dinitrate 2-phenyl-9-diethylaminoethylimidazo[1,2-a] benzimidazole to suppress basal and histamine-stimulated secretion of hydrochloric acid in a model of a continuous gastric perfusion.

The results are consistent with the specific pharmacological activity of H2-histamine-blocking action of the studied compound identified in the course of a comprehensive study of the receptor effect on isolated atrial tissues.

However, taking into account the fact that the receptor effect did not exceed the Ranitidine indices, the results obtained in vivo demonstrating a more pronounced suppression of acid production, may be associated with the presence of additional mechanisms of influence on the secretion of hydrochloric acid, which creates the preconditions for further studies.

CONCLUSIONS

Thus, the substance of dinitrate 2-phenyl-9-diethylaminoethylimidazo[1,2-a]benzimidazole at the dose of 30 mg/kg and its finished dosage form at the doses equal to ED50, has an antisecretory activity, statistically reliably superior to the average Ranitidine H2-histamine-blocking agent twice on average, at the level of both – basal and histamine-stimulated – secretion. The finished dosage form in the administrated doses showed a generally comparable pharmacological effect compared with the data obtained in the study of the substance, as adjusted for the calculated nature of the ED50 values. The obtained results provide a sufficient justification for further study of the possibility of using the substance and the finished dosage form of dinitrate 2-phenyl-9-diethylaminoethylimidazo[1,2-a]benzimidazole as an effective pharmaco-therapeutic agent for acid-dependent diseases of the gastrointestinal tract.

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