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ANTIULCER ACTIVITY OF 2-PHENYL-9-DIETHYLAMINO-ETHYLIMIDAZO[1,2-A]BENZIMIDAZOLE DINITRATE IN ETHANOL-PREDNISOLONE DAMAGE TO GASTRIC MUCOSA

M.V. Chernikov, M.A. Oganova, S.A. Kalashnikova, L.V. Polyakova, N.A. Khromova

Pyatigorsk Medical and Pharmaceutical Institute – branch of Volgograd State Medical University
11, Kalinin ave., Pyatigorsk, Russia 357532

E-mail: pharmax@list.ru

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Nowadays, the search for new effective and safe medicines for the treatment of acid-dependent gastrointestinal diseases remains an urgent problem of modern pharmacology.

The aim of this study was an experimentally study of the anti-ulcer activity of 2-phenyl-9-diethylaminoethylimidazo[1,2-a]benzimidazole dinitrate on the model of damage to the gastric mucosa caused by the administration of 80% ethanol and prednisolone combination (20 mg/kg).

Materials and methods. To simulate the damage to the gastric mucosa, the experimental animals (white male Wistar rats) were administrated with prednisone at the rate of 20 mg/kg and 80% ethyl alcohol at the dose of 0.6 ml/100 g of the animal body weight. Prednisolone was dissolved in 80% alcohol. Antisecretory antiulcer agents actively used in clinical practice, were selected as reference drugs: ranitidine (30 mg/kg, 10 mg/kg and 3 mg/kg) and omeprazole (3 mg/kg, 1 mg/kg and 0.3 mg/kg). The studied compound was used at the doses of 30 mg/kg, 10 mg/kg and 3 mg/kg. All the substances under study were administered intragastrically with the use of an atraumatic probe.

Results. It has been established that the benzimidazole derivative in the studied doses contributes to a dose-dependent reliable reduction in the area and depth of ulcerative lesions of the gastric mucosae relative to the control and reference drugs (ranitidine and omeprazole). In addition, in the maximum studied dose (30 mg/kg), the proportion of the animals with ulcerative lesions significantly decreases by more than 2 times. The calculated ED_{50} values for the benzimidazole derivative and ranitidine were 5.09 mg/kg and 38.23 mg/kg, respectively.

Conclusion. The obtained experimental data indicate that the benzimidazole derivative has a pronounced dose-dependent antiulcer effect on the model of ethanol-prednisolone erosive-ulcerous defects of the rats' gastric mucosae, which is superior to the effects of the reference preparations. It makes its further study promising.

Keywords: 2-phenyl-9-diethylaminoethylimidazo[1,2-a]benzimidazole dinitrate, antiulcer action, ethanol-prednisolone damages / injuries, preclinical studies

ПРОТИВОЯЗВЕННАЯ АКТИВНОСТЬ ДИНИТРАТА 2-ФЕНИЛ-9-ДИЭТИЛАМИНОЭТИЛИМИДАЗО[1,2-А] БЕНЗИМИДАЗОЛА ПРИ ЭТАНОЛ-ПРЕДНИЗОЛОНОВОМ ПОВРЕЖДЕНИИ СЛИЗИСТОЙ ОБОЛОЧКИ ЖЕЛУДКА

М.В. Черников, М.А. Оганова, С.А. Калашникова, Л.В. Полякова, Н.А. Хромова

Пятигорский медико-фармацевтический институт – филиал федерального государственного бюджетного образовательного учреждения высшего образования «Волгоградский государственный медицинский университет» Министерства здравоохранения Российской Федерации
357532, Россия, Ставропольский край, г. Пятигорск, пр. Калинина, 11

E-mail: pharmax@list.ru

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RESEARCH ARTICLE

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Поиск новых эффективных и безопасных лекарственных средств для лечения кислотозависимых заболеваний желудочно-кишечного тракта до настоящего времени остаётся актуальным вопросом фармакологии.

Цель данного исследования – экспериментальное изучение противоязвенной активности субстанции динитрата 2-фенил-9-диэтиламиноэтилимидазо[1,2-а]бензимидазола на модели повреждения слизистой оболочки желудка, вызванной введением комбинации 80% этанола и преднизолона (20 мг/кг).

Материалы и методы. Для моделирования повреждения слизистой оболочки желудка экспериментальным животным (белые крысы-самцы линии Wistar) вводили преднизолон из расчета 20 мг/кг и 80% этиловый спирт в дозе 0,6 мл на 100 г массы тела животных. Преднизолон растворяли в 80% спирте. В качестве препаратов сравнения были выбраны антисекреторные противоязвенные средства, активно применяемые в клинической практике: ранитидин (30 мг/кг, 10 мг/кг и 3 мг/кг) и омепразол (3 мг/кг, 1 мг/кг и 0,3 мг/кг). Изучаемое соединение использовалось в дозах 30 мг/кг, 10 мг/кг и 3 мг/кг. Все исследуемые вещества вводились внутрижелудочно с помощью атравматичного зонда.

Результаты и обсуждение. Установлено, что производное бензимидазола в исследуемых дозах способствует дозозависимому достоверному относительно контроля и препаратов сравнения (ранитидина и омепразола) снижению площади и глубины язвенных поражений слизистой оболочки желудка. Кроме того, в максимальной исследованной дозе (30 мг/кг) достоверно снижается более чем в 2 раза доля животных с язвенными поражениями. Расчетные значения $ЕД_{50}$ для производного бензимидазола и ранитидина составили 5,09 мг/кг и 38,23 мг/кг, соответственно.

Заключение. Полученные экспериментальные данные свидетельствуют о том, что производное бензимидазола оказывает выраженный дозозависимый противоязвенный эффект на модели этанол-преднизолоновых эрозивно-язвенных дефектов слизистой оболочки желудка крыс, превосходящий эффекты препаратов сравнения, что делает перспективным его дальнейшее изучение.

Ключевые слова: динитрат 2-фенил-9-диэтиламиноэтилимидазо[1,2-а]бензимидазола, противоязвенное действие, этанол-преднизолоновые повреждения, доклинические исследования

Список сокращений: СОЖ – слизистая оболочка желудка, СИ – степень изъязвления, ИИ – индекс изъязвления

INTRODUCTION

Nowadays, the search for new effective and safe medicines for the treatment of acid-dependent gastrointestinal diseases, remains an urgent problem of modern pharmacology [1, 2]. Chemical compounds from the group of benzimidazole derivatives, seem promising in terms of the development of new drugs, including those associated with an increase in acid production in the stomach [3, 4].

Nowadays, preclinical studies of the benzimidazole derivative, i.e., 2-phenyl-9-diethylaminoethylimidazo[1,2-a] benzimidazole dinitrate, which demonstrates antisecretory, antiulcer and gastroprotective effects in the experimental animal models of the laboratory pathologies associated with various pathogenetic mechanisms of ulcerogenesis in the gastric mucosae, are currently underway [5–7].

It is known that one of the mechanisms of the gastric ulcer formation is dissociation of the hypothalamic-pituitary-adrenal system of functions regulation caused by a chronic stress. In particular, an increased level of glucocorticoids, which cause an increase in catabolic processes that inhibit regeneration, disrupt microcirculation and stimulate the secretion of hydrochloric acid, provokes ulcerogenesis against the background of ischemia of the stomach wall [8, 9].

Moreover, under experimental conditions, the ulcer model caused by the action of the pure prednisolone glucocorticoid in its pure form, is characterized by low reproducibility. Therefore, a model modification had been used. It proposed a combination of prednisolone with 80% alcohol [10].

Ethanol contributes to the dissolution of the protective mucosal barrier, making the stomach wall vulnerable to damage by proteolytic and acidic factors. In addition, ethanol reduces the blood flow, damages the vascular endothelium, unbalances the cellular antioxidant defense, stimulating the formation of superoxidanion and hydroperoxide radicals [11].

Thus, the combination of ethanol and prednisone makes it possible to recreate erosive-ulcerous defects of the gastric mucosa with a high (100%) statistical probability.

The aim of this study was an experimentally study of the anti-ulcer activity of 2-phenyl-9-diethylaminoethylimidazo[1,2-a]benzimidazole dinitrate on the model of damage to the gastric mucosa caused by the administration of 80% ethanol and prednisolone combination (20 mg/kg).

MATERIALS AND METHODS

Animals

A study of the pharmacological activity was performed on outbred Wistar male rats (aged 10–12 weeks) weighing 180–250 g, obtained from the Rappolovo laboratory animal nursery (Rappolovo village, Leningrad region). At the time of the study, the rats were kept under standard vivarium conditions at the air temperature of 22 ± 20°C, the relative humidity of 60 ± 5% and a natural change in the daily cycle. Extruded food and tapwater were received by the rats ad libitum. The dispersion in the initial animals' mass in the group did not exceed 10% [12].

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)".

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

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European Convention for the protection of vertebrate animals used in experimental studies (1997) [13, 14].

Study design

The substance of 2-phenyl-9-diethylaminoethylimidazo[1,2-a]benzimidazole dinitrate was synthesized at the Scientific Research Institute of Physical & Organic Chemistry (FSAEI HE "Southern Federal University", Rostov-on-Don).

The evaluation of the antiulcer effect of the substances was carried out at the doses of 3 mg/kg, 10 mg/kg and 30 mg/kg. The omeprazole substance of 0.3 mg/kg, 1 mg/kg and 3 mg/kg (Sigma Aldrich, USA) and the ranitidine substance of 3 mg/kg, 10 mg/kg and 30 mg/kg (Sigma Aldrich, USA), were used as reference drugs.

The maximum volume of the drugs for the intragastric administration to the rats did not exceed 3 ml for the animals weighing up to 200 g, 5 ml for the animals from 200 to 240 g and 6 ml for the animals weighing more than 240 g.

Peptic ulcers were caused by the administration of prednisone at the rate of 20 mg/kg and 80% ethyl alcohol at the dose of 0.6 ml per 100 g of the animal body weight. Prednisolone was dissolved in 80% alcohol.

24 hours before the simulation of the pathology, the animals were subjected to a food deprivation with a free access to water.

In the experimental study, the animals had been divided into 10 groups of 10 individuals in each. The individuals of the control group were given a combination of ethanol and prednisone intragastrically as a single dose. In the experimental groups, the studied benzimidazole derivative and comparison preparations were administered 1 hour before the ethanol and prednisolone combination. The animals were euthanized 12 hours after the administration of the ethanol and prednisone combination.

After opening the abdominal cavities, the stomachs were removed and bathed with physiological saline. Then a macroscopic assessment of the mucous membrane was carried out, the tissues were photographed (macro photography). For histological studies, the stomachs were fixed in 10% neutral formalin and embedded in paraffin. Then, with the use of a sled microtome, the sections were prepared. They were stained with hematoxylin-eosin and probed microscopically. The process was followed by a description of the histological picture. Then the assessment of the depth of damage to the wall of the stomach was carried out.

Microphotography was performed using a LeicaDM 1000 microscope and the Leica Application Suite software package (Leica, Germany). The morphometric study was carried out using Leica Application Suite software tools, where the depth of the damage to the gastric mucosa was determined.

Defined indicators

To assess the severity of the damage in the study of the antiulcer action in the simulation of all pathological conditions, a point system was used [15].

In each group, the total score was calculated. The arithmetic mean value characterizing the average degree of ulceration in the group, was derived from that. In addition, the ulceration index was calculated in the group. The ulceration index reflects both the percentage of the frequency of animals with ulcers and the degree of degenerative disorders in the stomach. The depth of the damage was assessed by a histological examination.

According to the results of the study, the ED_{50} values were calculated for the benzimidazole derivative and for ranitidine, since they had been used in the same doses. The ED_{50} for omeprazole was not determined, since this substance has a different order of the doses used, and therefore, the comparison of the ED_{50} values as a criterion for evaluating the effectiveness, is incorrect.

Statistical processing

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

RESULTS

Macroscopically, this model reproduces the ulcerous defects affecting a significant area of the gastric mucosa, while both erosive and ulcerative lesions up to the necrotic ones, are clearly expressed.

The obtained experimental data showed that the benzimidazole derivative at the doses of 3, 10 and 30 mg/kg, contributes to the dose-dependent reliable control and reference drugs (ranitidine and omeprazole) reducing the ulcer lesions, the degree of perforation (DP) and the index of perforation (IP) by 35%, 74% and 91%, respectively. In these conditions, the proportion of the animals with ulcerative lesions of the gastric mucosa**e** reduced by 60% at the dose of 30 mg/kg (Table 1).

Ranitidine at the dose of 10 and 30 mg/kg also caused a significant decrease in the area of peptic ulcer lesions relative to the control. However, taking into account the degree of perforation points and the frequency of manifestations of peptic ulcers, the decrease in the index of perforation did not exceed 38% and 44%, respectively.

The administration of omeprazole at the doses of 1 and 3 mg/kg contributed significantly to the control decrease in the area of ulcerous defects, the degree of perforation and the index of perforation by 35% and 46%, respectively, while the proportion of the animals with ulcerative lesions of the gastric mucosae did not differ significantly from the control ones with the administration of both ranitidine and omeprazole (Table 1).

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Table 1 – Macroscopic analysis of the effect of the benzimidazole derivative substance and reference preparations on the gastric mucosae in response to the administration of the ethanol and prednisolone combination (male rats), n = 10, M ± m

Substance	Dose, mg/kg	Type of injury	Area of injury (mm^2/animal)	Proportion of animals with gastric mucosae (%)	Degree of perforation	Index of perforation	Index of perforation decline (%)
Control Ethanol + Prednisolone	–	Ulcers	88.9±25.7	100%	4.0 ±0.0	4.00	–
			36.7±15.9	90%			–
Benzimidazole derivative	3	Ulcers	23.7±15.1*	100%	2.6±0.4*	2,60	–35
		Erosions	16.3±6.5	90%			
	10	Ulcers	3.2±0.9*#&	70%	1.5±0.4*#	1.05	–74
		Erosions	7.9±5.8	80%			
	30	Ulcers	4,4±3,4*#&	40%	0.9±0.4*#	0.36	–91
		Erosions	16.3±7.1	80%			
Ranitidine	3	Ulcers	38.6±7.8	90%	3.3±0.4	2.97	–26
		Erosions	19,2±4,2	90%			
	10	Ulcers	28,5±6,2*	80%	3.1±0.5	2.48	–38
		Erosions	15.7±5.7	70%			
	30	Ulcers	18.1±5.6*	80%	2.8±0.6*	2.24	–44
		Erosions	27.1±9.3	70%			
Omeprazole	0,3	Ulcers	47.0±7.6	100%	3.9±0.1	3.90	–3
		Erosions	29.7±8.2	80%			
	1	Ulcers	42.9±10.8*	90%	2.9±0.5*	2.61	–35
		Erosions	28.2±8.8	80%			
	3	Ulcers	21.8±5.7*	80%	2.7±0.5*	2.16	–46
		Erosions	17.6±6.7	70%			

Note: * – significantly relative to control, P <0.05; # – significantly relative to the group receiving ranitidine, P <0.05; & – significantly relative to the group receiving omeprazole, P <0.05.

Table 2 – Results of morphometric assessment of the benzimidazole derivative and reference drugs' effect on the development of ulcerative lesions of the gastric mucosae in response to the administration of the ethanol (80%) and prednisolone 20 mg/kg (n = 50) combination

Group	Dose, mg/kg	Depth of injury, mkm	Average reduction in injury depth, %
Control (ethanol 80% + prednisolone 20 mg / kg)	–	311.22±9.83	–
Benzimidazole derivative	3.0	194.91±9.03*&	–38
	10.0	179.79±10.17*#&	–42
	30.0	89.76±10.27*#&	–71
Ranitidine	3.0	251.28±15.94*	–20
	10.0	283.03±21.53	–9
	30.0	282.33±22.11	–9
Omeprazole	0.3	225.76±12.48*	–28
	1.0	246.35±14.14*	–21
	3.0	189.55±16.95*	–39

Note: * – significantly relative to control, P <0.05; & – significantly relative to the group receiving ranitidine at the equivalent dose, P <0.05; # – significantly relative to the group receiving omeprazole at the equivalent dose, P <0.05

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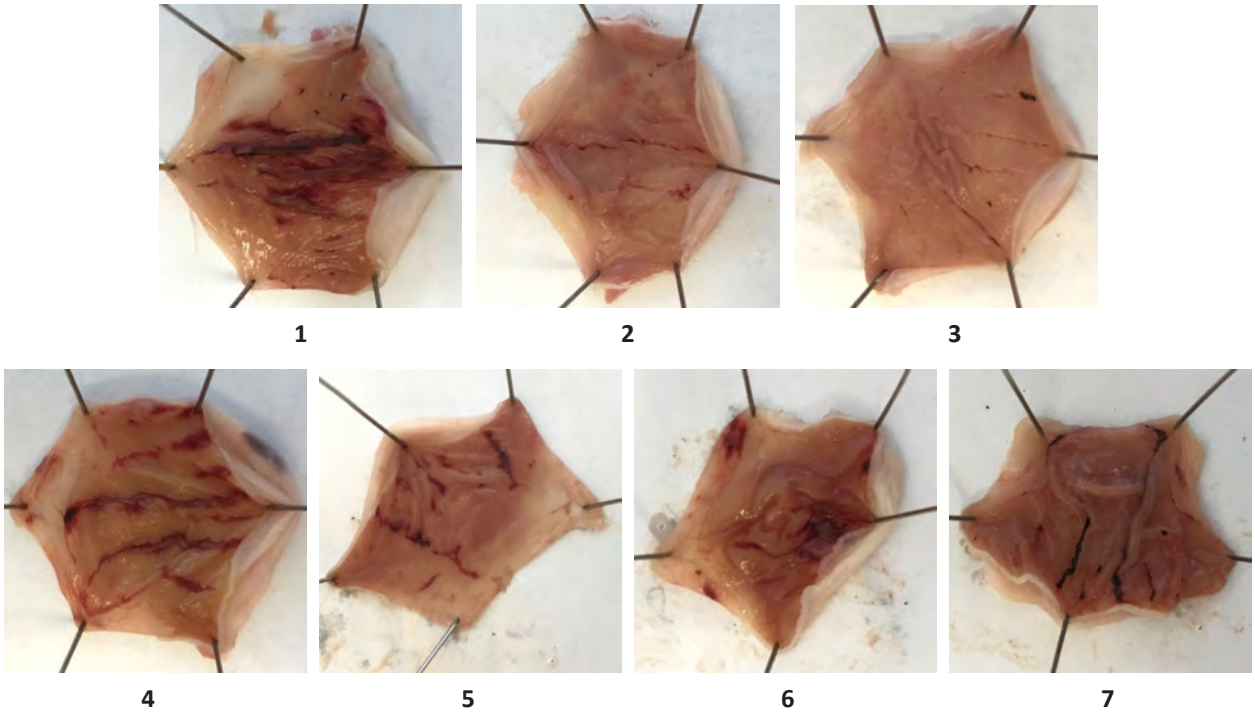

Figure 1 – Macrographs of the rats' stomachs in modeling erosions caused by the administration of the ethanol and prednisolone combination (natural scale):

Note: 1 – Control (ethanol + prednisolone), 2 – Benzimidazole derivative 10 mg/kg, 3 – Benzimidazole derivative 30 mg/kg, 4 – Ranitidine 10 mg/kg, 5 – Ranitidine 30 mg/kg, 6 – Omeprazole 1 mg/kg 7 – Omeprazole 3 mg/kg

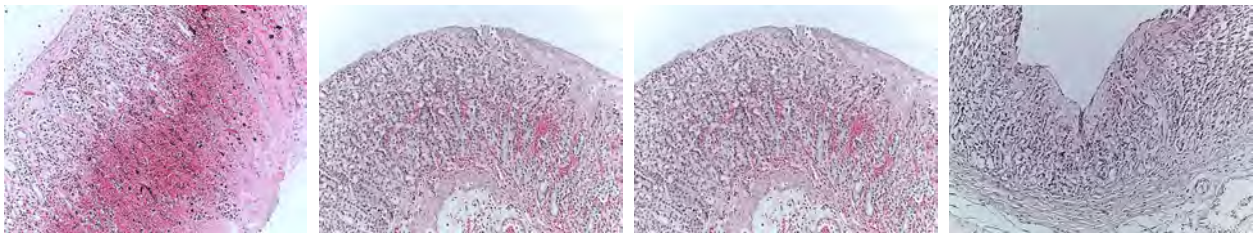

Figure 2 – Micrograph of the mucous membrane of the rats' stomachs in modeling erosions caused by the administration of the 80% ethanol and prednisolone (20 mg/kg) combination against the background of the benzimidazole derivate administration

Note: 1 – Control (ethanol + prednisone), 2 – Benzimidazole derivative 3 mg/kg, 3 – Benzimidazole derivative 10 mg/kg, 4 – Benzimidazole derivative 30 mg/kg

Thus, on the model of ethanol-prednisolone ulcers, the benzimidazole derivative had a pronounced antiulcer effect that exceeded the results in the ranitidine and omeprazole groups by an average of 2 times.

The calculated ED_{50} value for the benzimidazole derivative was 5.09 mg/kg, and the ED_{50} value for ranitidine was 38.23 mg/kg.

Fig. 1 shows the most typical macroscopic picture of the gastric mucosa against the background of the action of the studied substance of the benzimidazole derivative in comparison with ranitidine and omeprazole in modeling ethanol-prednisolone ulcerative lesions.

Histological studies showed that the combination of ethanol with prednisolone causes the development of extensive superficial defects of gastric mucosae with impressive zones of eosin masses affecting the submucosal base, profound leukocyte infiltration, hemorrhage and tissue necrosis (Fig. 2).

The benzimidazole derivative contributed to the dose-dependent decrease in the degree of mucosal injury, reduction of edema, hemorrhage, necrosis and destruction of blood vessels (Fig. 2).

In this model of injury, ranitidine and omeprazole showed a significantly less pronounced protective effect. The frequencies of the injuries reaching the submucosa, necrosis, destruction of glands and hemorrhages in the mucous membrane were comparable with the control (Fig. 3).

The results of morphometric studies indicate that the substance of the benzimidazole derivative at the doses of 3, 10 and 30 mg/kg contributed significantly to the control and reference drugs to reduce the injury depth by 38%, 42% and 71%, respectively (Table 2), significantly exceeding ranitidine and omeprazole effects.

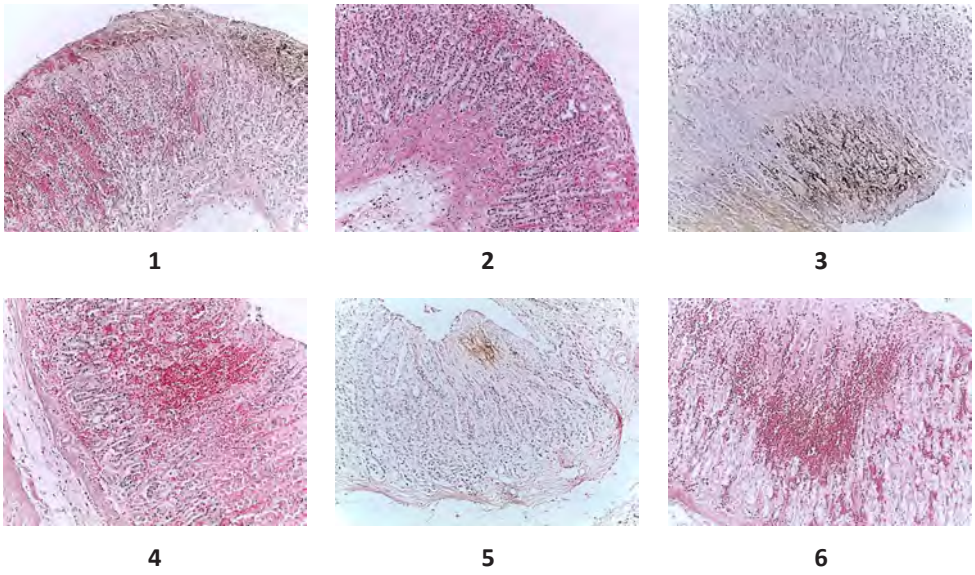

Figure 3 – Microphotographs of the mucous membrane of the rats' stomachs in modeling erosions caused by the administration of the 80% ethanol and prednisolone (20 mg/kg) combination against the background of the reference drugs administration

Note: 1 – Ranitidine 3 mg/kg, 2 – Omeprazole 0.3 mg/kg, 3 – Ranitidine 10 mg/kg, 4 – Omeprazole 1 mg/kg, 5 – Ranitidine 30 mg/kg, 6 – Omeprazole 3 mg/kg

DISCUSSION

The mechanism of the damaging effect of glucocorticoids on the gastric mucosa is in reducing the resistance of the protective barrier by inhibiting the synthesis of prostaglandins, which have a gastroprotective effect. It is also in inhibiting the activity of peroxidase, which leads to an increase in the level of H_2O_2 and, accordingly, the level of hydroxyl radicals, which, in their turns, enhances the gastric mucosa injury with hydrochloric acid secreted by the parietal cells of the stomach [16]. Glucocorticoids also slow down the repair and regeneration of the gastric mucosa by inhibiting angiogenesis [17], suppressing EGF-stimulated proliferation of the gastric mucosa epithelial cells, and under these circumstances one of the ways is to inhibit the activation of ERK1/ERK2, followed by suppression of COX-2 and a decrease in Cyclin D1 expression and DNA synthesis [18]. Ethanol, in its turn, helps to dissolve the protective mucous barrier, reduces the blood flow, damages the vascular endothelium and stimulates the formation of superoxide anion and hydroperoxide radicals [11]. The studied pharmaceutical substance of 2-phenyl-9-diethylaminoethylimidazo[1,2-a]benzimidazole dinitrate has shown a pronounced dose-dependent antiulcer effect in modeling a gastric mucosa injury caused by a combination of 80% ethanol and prednisolone. It has been recorded at both – macro- and micro-morphological levels, reducing the area and degree of the damage to the gastric mucosa, reducing edema, the intensity of hemorrhages, necrosis and destruction of blood vessels. Under these circumstances, the data obtained are consistent with the results of several previous studies, indicating the presence of antiulcer and gastroprotective effects under the conditions of reproduction of helicobacter-like damage in rats modeled by intragastric administration of ammonia in combination with acute dosed blood loss [5] and immobilization stress [6].

The antiulcer action of the benzimidazole derivative can be associated with several mechanisms. First, it is due to the pronounced antisecretory effect, manifested by suppression of HCl secretion, both basal and under the conditions of stimulation with histamine [7]. It leads to a decrease in the acidity of the gastric contents and, accordingly, a decrease in its ulcerogenic potential. Second, it is connected with the probable antioxidant activity, which is shown in a number of studies on the biological activity of benzimidazole derivatives [19–21], which, however, requires additional studying.

CONCLUSION

The obtained experimental data indicate that the benzimidazole derivative has a pronounced dose-dependent antiulcer effect on the model of ethanol-prednisolone erosive-ulcerous defects of the gastric mucosa, on average 2 times greater than the effects of the reference drugs.

The research results are consistent with the previously obtained data on the antisecretory and antiulcer activity of 2-phenyl-9-diethylaminoethylimidazo[1,2-a] benzimidazole dinitrate. A further study of the pharmacological effects of this compound in order to create a new antisecretory antiulcer drug, can be suggested as promising if we take into consideration the level of anti-ulcerogenic effect exceeding that of the reference drugs widely used in clinical practice, H_2-histamine blocker ranitidine and an inhibitor of hydrogen-potassium ATPase omeprazole.

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AUTHOR’S CONTRIBUTION

All the authors have equally contributed to the research work.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Maev IV, Andreev DN, Zaborovsky AV. Basics of gastric acid secretion. Medical Council. 2018;(3):7–14. Doi:https://doi.org/10.21518/2079-701X-2018-3-7-14. (in Russ)
2. Schubert ML. Physiologic, pathophysiologic, and pharmacologic regulation of gastric acid secretion. Curr Opin Gastroenterol. 2017;33(6):430–8. doi: 10.1097/MOG.0000000000000392.
3. Salahuddin A, Shaharyar M, Mazumder A. Benzimidazoles: A biologically active compounds. Arabian J Chem. 2017;10:157–73.
4. Hockley MH, Titman RB. Antiulcer benzimidazole derivatives. Patent US 4767769 A; No US 07/065,363; 30 Aug 1988. Available at: https://patents.google.com/patent/US4767769A/en
5. Spasov AA, Petrov VI, Anisimova VA, Minkin VI, Chernikov MV. Lekarstvennaya substantsiya dlya podavleniya gelikobakteropodobnykh erozivno-yazvennykh povrezhdeniy slizistoy obolochki zheludka [Drug substance for suppressing helicobacter-like erosive and ulcerative lesions of the gastric mucosa]. Patent RU 2395282 C2. Bul. No21; 2010. (in Russ)
6. Chernikov MV, Oganova MA, Gerasimenko AS, Artemyev EA. Antiulcer activity of dinitrate 2-phenyl-9diethylaminoethylamine[1,2-a]benzimidazole with helicobacter pylori-like damage of gastric mucosa. Pharmacy & Pharmacology. 2018;6(4):367–79. Doi: https://doi.org/10.19163/2307-9266-2018-6-4-367-379.
7. Chernikov MV, Oganova MA, Gerasimenko AS, Artemyev EA. Study of antisecretory activity of dinitrate 2-phenyl-9-diethylaminoethylimidazo[1,2-a]benzimidazole by method of continuous perfusion of rats’ stomachs. Pharmacy & Pharmacology. 2019;7(4):231–40. Doi: https://doi.org/10.19163/2307-9266-2019-7-4-231240.
8. Caplan A, Fett N, Rosenbach M, Werth VP, Micheletti RG. Prevention and management of glucocorticoid-induced side effects: A comprehensive review: Gastrointestinal and endocrinologic side effects. J Am Acad Dermatol. 2017;76(1):11–6.
9. Podvigina TT, Filaretova LP. Dvoystvennyye effekty glyukokortikoidnykh gormonov na slizistuyu obolochku zheludka [Dual Effects of Glucocorticoids on the Gastric Mucosa]. Advances in Physiological Sciences 2014;45(4):19–33. (in Russ)
10. Baginskaya AI, Ferubko EV, Kurmanova EN, Voskoboinikova IV, Kolkhir VK. Eksperimental’noye modelirovaniye v gastroenterologii. Prakticheskiye rekomendatsii. Chast’ II. Eksperimental’nyye modeli «ostrykh» yazv zheludka [Experimental modelling in gastroenterology. Practical guidelines. Part II. Experimental models of acute ulcer lesions of the stomach]. Problems of Biological, Medical and Pharmaceutical Chemistry. 2016;3:32–40. (in Russ)
11. Simoes S, Lopes R, Campos MCD, Marruz MJ, da Cruz MEM, Corvo L. Animal models of acute gastric mucosal injury: Macroscopic and microscopic evaluation. Animal Model Exp Med. 2019;2:121–6.
12. Rukovodstvo po provedeniyu doklinicheskikh issledovaniy lekarstvennykh sredstv. Chast’ pervaya [Guidelines for preclinical studies of drugs. Part One]. Ed. A.N. Mironov, N.D. Bunatyan, A.N. Vasiliev et al. Moscow, Grif & K; 2012: 944 p. (in Russ)
13. GOST R 33044–2014. Printsipy nadlezhashchey laboratornoy praktiki [Principles of Good Laboratory Practice]. (OECD Guide 1: 1998, IDT). Moscow, Standartinform; 2015:11 p. (in Russ)
14. Order of the Ministry of Health of the Russian Federation of April 1, 2016 N 199n “On the Approval of the Rules of Good Laboratory Practice” (Registered in the Ministry of Justice of the Russian Federation on August 15, 2016 N 43232). Bulletin of regulatory acts of federal executive bodies, N 37, 2016. (in Russ)
15. Adinortey MB, Ansah C, Galyuon I, Nyarko A. In vivo models used for evaluation of potential antigastroduodenal ulcer. Ulcers. 2013;2013:1–12. Doi: http://dx.doi.org/10.1155/2013/796405.
16. Viswanatha Swamy AHM, Sajjan M, Thippeswamy AHM, Koti BC, Sadiq AJ. Influence of Proton Pump Inhibitors on Dexamethasone-Induced Gastric Mucosal Damage in Rats. Indian J Pharm Sci. 2011;73(2):193–8. Doi: 10.4103/0250-474x.91582
17. Luo JC, Shin VY, Liu ES. et al. Dexamethasone delays ulcer healing by inhibition of angiogenesis in rat stomachs. Eur J Pharmacol, 2004;485:275–81. Doi: 10.1016/j.ejphar.2003.11.038.
18. Luo JC, Chi CW, Lin HY. et al. Dexamethasone inhibits epidermal growth factor-stimulated gastric epithelial cell proliferation. J Pharmacol Exp Ther. 2007;320:687–94. DOI: 10.1124/jpet.106.113035
19. Zhou B, Li B, Yi W, et al. Synthesis, antioxidant, and antimicrobial evaluation of some 2-arylbenzimidazole derivatives. Bioorg Med Chem Lett. 2013;23(13):3759-63. doi: 10.1016/j.bmcl.2013.05.004.
20. Ates-Alagoz Z. Antioxidant activities of retinoidal benzimidazole or indole derivatives in In vitro model systems. Current Med. Chem. 2013; 20(36):4633–9. Doi: 10.1016/j.bmcl.2013.05.004
21. Gaba M, Singh S, Mohan C, et al. Design, Synthesis and Pharmacological Evaluation of Gastro-protective Anti-inflammatory Analgesic Agents based on Dual Oxidative Stress. Cyclooxygenase Inhibition. Antiinflamm Antiallergy Agents Med. Chem. 2019. Doi: 10.2174/1871523018666190325155244.

AUTHORS

Maxim V. Chernikov – Doctor of Sciences (Medicine), Associate Professor, Head of the Department of Biology, Pyatigorsk Medical and Pharmaceutical Institute – branch of Volgograd State Medical University. Research interests: pharmacology, clinical pharmacology. ORCID 000-0001-8340-1296. E-mail: pharmax@list.ru

Marina A. Oganova – Candidate of Sciences (Pharmacy), Associate Professor of the Department of Biology, Pyatigorsk Medical and Pharmaceutical Institute – branch of Volgograd State Medical University. Research interests: pharmacology, clinical pharmacology. E-mail: marina-oganova81@mail.ru

Svetlana A. Kalashnikova – Doctor of Sciences (Medicine), Professor, Head of the Department of Morphology, Pyatigorsk Medical and Pharmaceutical Institute – branch of Volgograd State Medical University. ORCID 0000-0002-7688-9366. E-mail: kalashnikova-sa@yandex.ru

Lyudmila V. Polyakova – Candidate of Sciences (Medicine), Associate Professor, Department of Morphology, Pyatigorsk Medical and Pharmaceutical Institute – branch of Volgograd State Medical University. ORCID 0000-0002-7688-9366. E-mail: lypolyakova7@gmail.ru

Natalya A. Khromova – Postgraduate Student, Department of Biology and Physiology**,** Pyatigorsk Medical and Pharmaceutical Institute – branch of Volgograd State Medical University. E-mail: khromovanatasha1994@gmail.com