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Results of Preclinical Studies of 4-(2-(4-nitrophenyl)-2-oxoethyl)-1-(thietane-3-yl)-1H-1,2,4-triazole-4-th Bromide in Relation to the Hemostasis System *in vivo*

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Abstract

Introduction. A characteristic manifestation of vascular brain damage is depressive disorders that accompany both acute and chronic disorders of cerebral circulation. Depression not only reduces the patient's quality of life, but also complicates the treatment of basic vascular disease, increases the risk of stroke and death. Therefore, complex therapy of vascular depression includes not only antidepressants, but also basic means to correct the consequences of disorders of cerebral blood flow, including with antiplatelet activity. In this regard, the development of a new molecule based on thietane-containing heterocycles, combining the properties of an antidepressant and an antiplatelet agent.

Aim. To conduct a preclinical evaluation of 4-(2-(4-nitrophenyl)-2-oxoethyl)-1-(thietane-3-yl)-1H-1,2,4-triazol-4 bromide when administered to rats.

Materials and methods. A study was conducted of the effect of 4-(2-(4-nitrophenyl)-2-oxoethyl)-1-(thietan-3-yl)-1H-1,2,4-triazol-4-bromide on the hemostasis system during intravenous and intragastric administration to healthy white non-linear sexually mature male rats ($n = 160$). Thromboelastography was performed on a TEG 5000 device, activated with a 0.2 M solution of calcium chloride, Born aggregometry and standard clotting tests to assess the coagulation component of hemostasis.

Result and discussion. The findings show that 4-(2-(4-nitrophenyl)-2-oxoethyl)-1-(thietane-3-yl)-1H-1,2,4-triazole-4-th bromide with peroral administration exceeded acetylsalicylic acid by 2.8 times in terms of ED50, and by 1.8 times with intravenous way of administration accordingly. A similar effect of pentoxifylline in the intravenous route of administration was recorded at a concentration of 27.8 mg/kg versus 12.4 mg/kg of compound I. The results of a complex method to assess the state of the hemostasis system indicate a more pronounced antiaggregational effect of compound I compared with pentoxifylline and acetylsalicylic acid.

Conclusion. Preclinical studies of 4-(2-(4-nitrophenyl)-2-oxoethyl)-1-(thietane-3-yl)-1H-1,2,4-triazole-4 bromide, was demonstrated that a combination of antidepressant and antiplatelet activity, which can serve as a basis for further drug development.

Keywords: derivatives of 3-substituted thietanes, antiaggregational activity

Conflict of interest. The authors declare that they have no obvious and potential conflicts of interest related to the publication of this article.

Contribution of the authors. Yi Wang, Nailya R. Bulatova, Aleksandr V. Samorodov invented and developed an experiment. Elena E. Klen, Galina A. Rosit synthesized samples. Elena A. Smolyarchuk, Ksenia A. Zavadich participated in data processing. Irina L. Nikitina, Irina D. Krylova carried out theoretical calculations. All the authors participated in the discussion of the results and in writing the text of the article.

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Результаты доклинических исследований 4-(2-(4-нитрофенил)-2-оксоэтил)-1-(тиетан-3-ил)-1H-1,2,4-триазол-4-ия бромида в отношении системы гемостаза в условиях *in vivo*

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Резюме

Введение. Характерным проявлением сосудистого поражения головного мозга являются депрессивные расстройства, которые сопутствуют как острым, так и хроническим нарушениям мозгового кровообращения. Депрессия не только снижает качество жизни пациента, но и затрудняет лечение базисного сосудистого заболевания, повышает риск развития инсульта и летального исхода. Поэтому комплексная терапия сосудистой депрессии включает не только антидепрессанты, но и базисные средства для коррекции последствий нарушений мозгового кровотока, в том числе с антиагрегантной активностью. В этой связи разработка новой молекулы на основе тиетансодержащих гетероциклов, сочетающей в себе свойства антидепрессанта и антиагреганта.

Цель. Провести доклиническую оценку 4-(2-(4-нитрофенил)-2-оксоэтил)-1-(тиетан-3-ил)-1Н-1,2,4-триазол-4-ия бромида при введении крысам.

Материалы и методы. Проведено исследование влияния 4-(2-(4-нитрофенил)-2-оксоэтил)-1-(тиетан-3-ил)-1Н-1,2,4-триазол-4-ия бромида на систему гемостаза при внутривенном и внутрижелудочном введении здоровым белым нелинейным половозрелым крысам-самцам (n = 160). Проводилась тромбоэластография на аппарате TEG 5000, активированная 0,2 М раствором хлорида кальция, агрегатометрия по Born и стандартные клоттинговые тесты по оценке коагуляционного звена гемостаза.

Результаты и обсуждение. Установлено, что 4-(2-(4-нитрофенил)-2-оксоэтил)-1-(тиетан-3-ил)-1Н-1,2,4-триазол-4-ия бромида при пероральном введении превосходило по уровню ED50 ацетилсалициловую кислоту в 2,8 раза, а при внутривенном пути введения в 1,8 раза соответственно. Аналогичный эффект пентоксифиллина при внутривенном пути введения регистрировался в концентрации 27,8 мг/кг против 12,4 мг/кг соединения I. Результаты комплексного метода оценки состояния системы гемостаза – тромбоэластографии, свидетельствуют о более выраженном антиагрегационном действии данного соединения по сравнению с пентоксифиллином и ацетилсалициловой кислотой.

Заключение. Таким образом, в результате доклинических исследований 4-(2-(4-нитрофенил)-2-оксоэтил)-1-(тиетан-3-ил)-1Н-1,2,4-триазол-4-ия бромида установлено сочетание антидепресивной и антиагрегационной активности, что может послужить основой для дальнейшей разработки лекарственных препаратов.

Ключевые слова: производные 3-замещенных тиетанов, антиагрегационная активность

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Вклад авторов. Ю. Ванг, Н. Р. Булатова, А. В. Самородов придумали и разработали эксперимент. Е. Э. Клен, Г. А. Розит синтезировали образцы. Е. А. Смолярчук, К. А. Завадич – участвовали в обработке данных. И. Л. Никитина, И. Д. Крылова проводили теоретические расчеты. Все авторы участвовали в обсуждении результатов и написании текста статьи.

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INTRODUCTION

Disorders in the hemostatic system cause a wide prevalence of thrombosis of various origins and are a key link in the pathogenesis of many diseases and critical conditions. The need to pharmacologically correct the hemostatic system and the degree of their efficacy is a fact proven by the results of more than 280 meta-analyses for secondary and 6 tests for primary prevention of thrombosis [1–4]. To date, there are schemes to treat and prevent thrombosis of various localization, based on the results of clinical studies [5–7]. Thrombosis and thromboembolic complications are still widespread and high in frequency, being one of the main causes of mortality and disability of the adult population in industrialized countries [8, 9]. This is a consequence of the general aging of the population [10], the growth of oncological diseases [11, 12], an increase in the number of overweight and diabetic patients [13–15], an increase in the number of patients requiring long hospital stays [16, 17], or/and patients requiring emergency surgical interventions [18–20] and other population

factors, as well as insufficient efficacy, high frequency of side effects and lack of selectivity for the hemostasis system of currently used drugs [21–23]. According to WHO forecasts, by 2030, acute cerebrovascular accidents (ACVA) will take a leading position among the causes of the burden of diseases on a global scale. Therefore, complex therapy of vascular depression includes not only antidepressants, but also basic means to correct the consequences of disorders of cerebral blood flow, including with antiplatelet activity. In this regard, developing a new molecule based on thietane-containing heterocycles, combining the properties of an antidepressant and an antiplatelet agent, will qualitatively enhance the effectiveness of therapy for patients with ACVA due to multimodal action. Synthesis of analogues and derivatives of used drugs is one of the modern directions in the development of new medicines. The earlier findings aimed at searching for potential antiplatelet agents in a number of newly synthesized 3-substituted thietanes demonstrate pronounced antidepressant activity [24] and antiplatelet activity in some compounds of this series *in vitro* [25–27].

Purpose of the work is: to conduct a preclinical evaluation of 4-(2-(4-nitrophenyl)-2-oxoethyl)-1-(thietane-3-yl)-1H-1,2,4-triazol-4 bromide (compound I) when administered to rats (figure 1).

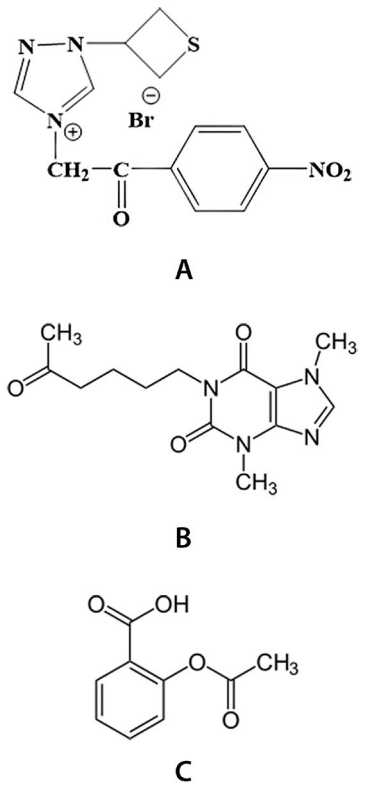

Figure 1. Structural formula of compound I (A), pentoxifylline (B) and acetylsalicylic acid (C)

MATERIALS AND METHODS

The experimental work was carried out in accordance with the recommendations of the «Guidelines for the preclinical study of new pharmacological substances» [28]. Taking into account the «principle of chemical similarity» and the potential scope of application of this compound as a means to correct depression caused by disorders of cerebral circulation[1], 3,7-dimethyl-1-(5-oxohexyl)xanthine were selected as comparison drugs at this stage of the study (Pentoxifylline, JSC Dalkhimpharm, Russia, series N 290719, expiration date: 08.2022, produced: 07.2024) [29] and acetylsalicylic acid (Shandong Xinhua Pharmaceutical Co., Ltd., China, series N 10L16, expiration date: 04.2022, produced: 10.11.2020) [2].

Experimental studies *in vivo* were performed on 160 white nonlinear mature male rats aged 3.5–4.0 months, weighing 225 ± 32 g. All experiments were performed in compliance with the European Convention for the Protection of Vertebrate Animals in Laboratory Conditions, the Rules for Conducting Laboratory preclinical studies in the Russian Federation. The study was approved by the ethics committee of the Bashkir State Medical University (protocol No. 2 of November 12, 2020).

Just before the experimental work, laboratory rats were divided into 4 groups of 20 animals each: group of administration of pentoxifylline, acetylsalicylic acid, group of compound I and group of control rats. The animals were anesthetized with sodium thiopental (40 mg/kg), blood was taken from the jugular vein.

Thromboelastography was carried out with TEG 5000 (Haemoscope Corporation, United States). For TEG activator was used 0,2 M solution $CaCl_2$ (LLC "Technology-Standard", Russia).

The study of platelet aggregation function was studied on the "AT-02" (LLC "NPF Meditsina-Technika", Russia). Adenosine diphosphate (ADP) at a concentration of 20 μg/ml and collagen – 5 mg/ml produced by LLC "Technologiya-Standard" (Russia) were used as inducers of platelet aggregation [30].

Anticoagulation activity (activated partial thromboplastin time (APTT), prothrombin time (PTT), thrombin time (TT), antithrombin III (ATIII) and A. Clauss fibrinogen concentration) was determined by generally recognized clotting tests on a turbidimetric hemocoagulometer Solar CGL 2110 (CJSC "SOLAR", Russia) [2].

The findings were processed using the STATISTICA 10.0 statistical package (StatSoft Inc., USA) and GraphPad Prism (GraphPad Software, Inc., USA). Verification of the normality of the distribution of the actual data was performed using the Shapiro-Wilk criterion. Median and interquartile interval were used to describe the groups. The analysis of variance was carried out using the Kraskel-Wallis or Mann-Whitney criteria. The critical significance level p for statistical criteria was assumed to be 0.05. The IC50 and ED50 values were calculated using

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nonlinear fitting of curves describing antiaggregational activity (%) according to a logarithmic equation with 4 parameters using GraphPad Prism software.

RESULT AND DISCUSSION

The first stage of the study evaluated the ED50 antiaggregational activity at various routes of administration of the studied compound and comparison drugs. The results of evaluating the effect of compound I on platelet aggregation during intravenous and intragastric administration to intact rats are presented in Table 1.

Table 1. Antiaggregational activity (ED_{50}) of comparison drugs and compound I during intragastric and intravenous administration to rats

Medicament	Orally, mg/kg	Intravenously, mg/kg
Acetylsalicylic acid	24.1	21.7
Pentoxifylline	–	39.8
Compound I	8.5	12.4

The data in Table 1 show that compound I, when administered orally, exceeded acetylsalicylic acid by 2.8 times in terms of ED_{50}, and by 1.8 times in the intravenous route of administration, respectively. A similar effect of pentoxifylline in the intravenous route of administration was recorded at a concentration of 27.8 mg/kg versus 12.4 mg/ kg of compound I.

The second stage assessed the effect on the hemostasis system by a global test – thromboelastography and standard clotting tests. Studies of antiaggregational activity at this stage were carried out with intravenous administration to rats in equimolar doses equal to 40.0 mg/kg for pentoxifylline, 25.9 mg/kg for acetylsalicylic acid and 55.3 mg/kg for compound I.

The results of assessing the effect of compound I on the hemostasis system by thromboelastography, which allows evaluating the hemostasis system in a complex by the main key links, are presented in table 2.

Thromboelastograms of rats receiving intravenous pentoxifylline or acetylsalicylic acid, show a shift in the total coagulation potential towards hypocoagulation: the median thrombodynamic potential index (TPI) in the control group is 15.1/sec, and in the group of pentoxifylline and acetylsalicylic acid is 7.7 ($p < 0.05$) and 5.6 ($p < 0.05$) /sec, respectively. The MA parameter characterizing the functional activity of platelets in the group of rats treated with pentoxifylline or acetylsalicylic acid was 11.2 % ($p < 0.05$) and 36.7 % ($p < 0.05$), respectively, less in comparison with the control. At the same time, the Angle indicator, reflecting the functional state of fibrinogen, remains at the level of control values when administered to animals (43.7 in the control vs 39.9 for pentoxifylline and 34.6 for acetylsalicylic acid; $p > 0.05$).

Comparison of the data of thrombelastograms for groups of rats that received compound I allows us to draw the following conclusions. The results of a complex method to assess the state of the hemostasis system indicate a more pronounced antiaggregational effect of compound I compared with pentoxifylline and acetylsalicylic acid. The MA index decreases in the group of rats treated with compound I by 1.6 times ($p < 0.05$) compared with the pentoxifylline group and by 1.2 times ($p < 0.05$) compared with acetylsalicylic acid. The mechanical and physical properties of the clot also change: the G index decreases in the group of compound I by 1.7 and 1.3 times ($p < 0.05$) compared with the indicators of pentoxifylline and acetylsalicylic acid, respectively. The fibrinolysis indices (CLT and CL30%) in the presence of pentoxifylline and compound I remain at the control values.

The next stage of the experiments evaluated the effect of compound I and antiplatelet agents on the coagulation component of hemostasis and markers of thrombosis (table 3).

Table 2. Indicators of thromboelastography during intravenous administration of compound I and comparison drugs to rats, Me [0.25–0.75]

Indicator	Control	Pentoxifylline	Acetylsalicylic acid	Compound I
R (time of latency from start of test to initial fibrin formation), sec	11.6 (9.7–13.2)	9.9 (8.5–11.4)	10.2 (8.7–11.1)	13.8 (10.6–14.2)
Angle (measures the speed at which fibrin build up and cross-linking takes place, hence assesses the rate of clot formation), deg	43.7 (42.4–44.3)	39.9 (36.4–45.1)	34.6 (33.9–44.5)	41.4 (38.6–43.1)
MA (maximum amplitude), mm	55.9 (51.2–57.8)	49.6 (46.7–52.3)*	35.4 (32.1–37.2)*	31.5 (28.4–33.2)*,‡
TMA (time to maximum amplitude), min	35.4 (32.4–38.5)	33.4 (32.5–37.3)	38.4 (37.4–41.3)	42.5 (40.5–43.8)*,‡
G (shear modulus strength), dyne/cm^2	6.3 (5.7–6.4)	4.6 (4.1–6.3)*	3.5 (3.2–3.9)*	2.7 (2.2–3.4)*,‡,Δ
E (elasticity constant), dyne/cm^2	127.3 (115.4–142.3)	101.5 (98.5–109.4)*	113.4 (101.8–116.7)*	67.3 (64.8–71.0)*,‡,Δ
TPI (thrombodynamic potential index), sec	15.1 (13.2–17.1)	7.7 (7.1–8.6)*	5.6 (5.1–6.3)*	3.4 (2.7–4.1)*,‡,Δ
CL30 (clot lysis index at 30 minute), %	97.5 (91.3–99.5)	98.5 (97.3–99.2)	99.4 (97.8–99.7)	98.8 (97.5–99.3)
CLT (clot lysis time), min	36.9 (32.4–38.3)	36.5 (33.1–38.4)	36.5 (33.1–38.4)	34.4 (30.1–36.5)
CI (clotting or coagulation index)	0.38 (0.1–0.7)	–1.8 (–1.1/–2.7)*	–2.3 (–2.1/–2.6)*	–4.1 (–3.5/–5.7)*,‡,Δ

Note. * – $p < 0.05$ – pentoxifylline/acetylsalicylic acid/compound I vs control; ‡ – $p < 0.05$ – pentoxifylline vs compound I; Δ – $p < 0.05$ – acetylsalicylic acid vs compound I, $n = 20$.

Table 3. Indicators of coagulation component of hemostasis during intravenous administration of compound I and comparison drugs to rats, Me [0.25-0.75]

№	Indicator	Control	Pentoxifylline	Acetylsalicylic acid	Compound I
1	APPT, sec	24.2 (21.5–26.3)	23.5 (21.4–24.9)	21.7 (20.4–24.1)	23.9 (22.1–24.7)
2	TT, sec	28.1 (25.9–29.4)	28.4 (27.2–29.4)	27.8 (25.3–28.7)	26.9 (25.7–28.4)
3	PTT, sec	13.2 (11.7–13.4)	12.9 (11.4–13.7)	13.4 (11.7–14.5)	14.1 (12.7–14.9)
4	Fibrinogen, sec	25.4 (22.7–26.4)	25.7 (24.7–26.5)	23.9 (22.8–24.7)	24.9 (23.5–26.8)
5	AT III, %	94.6 (94.8–97.3)	97.3 (96.3–98.1)	96.6 (94.5–97.2)	97.5 (94.5–98.9)

Note. $p > 0.05$ – pentoxifylline/acetylsalicylic acid/compound I vs control, $n = 20$.

The findings proved that pentoxifylline and acetylsalicylic acid naturally do not show activity against the coagulation link of the hemostasis system when administered to rats. The studied compound also has no effect on the activity of coagulation factors of the internal and external activation pathways and the concentration of fibrinogen according to Clauss.

Disturbances in the hemostasis system are a key link in the pathogenesis of many cardiovascular, cerebrovascular, immune, and infectious diseases. Much of the research currently focuses on the inhibition of platelet activation and aggregation. In our study, we chose pentoxifylline and acetylsalicylic acid as analogue drugs. Despite the fact that pentoxifylline is not an antithrombotic drug, today the indications for the use of pentoxifylline as a component of modern antithrombotic therapy are clearly defined. The results of randomized studies and clinical recommendations demonstrate the effectiveness of pentoxifylline specifically in cases of retinal vascular thrombosis and acute ischemic cerebrovascular accident [29]. Despite the high and seemingly obvious benefits of taking acetylsalicylic acid, according to the author [25], acetylsalicylic acid turns out to be ineffective in 5–48 % of cases of long-term use. The use of acetylsalicylic acid in combination with other drugs (clopidogrel, ticlid, etc.), which have an inhibitory effect on platelet activation processes, statistically reduces the frequency of repeated fatal episodes of myocardial infarction and stroke [27]. In this regard, the development of new drugs and evaluation of their antiaggregation effect seems quite promising. This is especially true in terms of the development of drugs for complex therapy of cerebrovascular accidents.

CONCLUSION

Thus, the preclinical findings of 4-(2-(4-nitrophenyl)-2-oxoethyl)-1-(thietane-3-yl)-1H-1,2,4-triazole-4-th bromide with intravenous and intragastric administration to rats, show that the level of its antiaggregational activity exceeds the indicators of an analog drug which, in combination with the previously established antidepressant activity, can serve as a basis for further drug development.

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