ФАРМАКОЛОГИЯ, КЛИНИЧЕСКАЯ ФАРМАКОЛОГИЯ / PHARMACOLOGY, CLINICAL PHARMACOLOGY

DOI: https://doi.org/10.60797/IRJ.2024.144.84

POSSIBILITIES OF INSTRUMENTAL MONITORING OF APIXABAN PHARMACODYNAMICS

Research article

Solovev M.A.[1,] *, Gulyaev N.I.[2], Zolotarev A.A.[3], Kotlovskaya L.Y.[4], Udut V.V.[5]

[1] ORCID : 0000-0001-6914-684X;

[2] ORCID : 0000-0002-7578-8715;

[3] ORCID : 0009-0004-8878-9524;

[4] ORCID : 0000-0001-7327-3980;

[5] ORCID : 0000-0002-3829-7132;

[1, 3, 4, 5] Tomsk National Research Medical Center of the Russian Academy of Sciences, Tomsk, Russian Federation

[2] National Medical Research Center for High Medical Technologies - Central Military Clinical Hospital named after A.A. Vishnevsky Ministry of Defense of Russia, Krasnogorsk, Russian Federation

* Corresponding author (m.a.solovyev[at]mail.ru)

Abstract

This study assessed pharmacokinetics and pharmacodynamics using low-frequency piezothromboelastography (LPTEG) and a validated HPLC-MS/MS technique in healthy volunteers receiving apixaban as anticoagulant therapy. At the 1-hour monitoring point, there was an increase in the concentration of 5 mg of apixaban taken to 97 [86;105] ng/ml. As described in the instructions for use, concentrations reached maximum values 4 hours after administration and amounted to (130 [117;144] ng/ml). The maximum concentration of the drug taken statistically significantly decreases to 120 [108;130] ng/ml on the 6th, to 97 [88;107] ng/ml on the 10th hour of observation, after 84 hours [75;93] ng/ ml at 12 hours and up to 19 [17;22] ng/ml at 24 hours. When studying using the LFPTEG method, we observe chronic and structural hypocoagulation in whole blood 2 hours after taking the drug, while the concentration of this anticoagulant is within 110 [99;121] ng/ml. Next, a hypocoagulation shift is formed, indicated by an increase in the “gelation” point at the three-hour monitoring point. At the same time, there is a decrease in the thrombin activity constant in relation to the initial values before taking apixaban ($p < 0.05$). At the 4-hour monitoring point, there is an increase in the “gelation” time with a decrease in the maximum amplitude, thrombin activity constant and coagulation activity index $p<0.05$), which allows us to judge the maximum expressed hypocoagulation state in the study volunteers. Next comes a decrease in the effect of apixaban, indicated by moderate structural hypocoagulation, which develops only into a tendency to control the effect of the drug for 10 hours. And after 12 hours, the indicators return to the original data before taking the anticoagulant. The results obtained allow us to conclude that it is possible to use LFPTEG technology to monitor the pharmacodynamics of apixaban, in contrast to standard control methods, in which efficacy results are available in the range of working concentrations of the drug in blood plasma from ~110 ng/ml and above.

Keywords: low-frequency piezothromboelastography, hemostatic potential, antithrombotic therapy, personification, apixaban, NOAC.

ВОЗМОЖНОСТИ ИНСТРУМЕНТАЛЬНОГО МОНИТОРИНГА ФАРМАКОДИНАМИКИ АПИКСАБАНА

Научная статья

Соловьев М.А.[1,] *, Гуляев Н.И.[2], Золотарев А.А.[3], Котловская Л.Ю.[4], Удут В.В.[5]

[1] ORCID : 0000-0001-6914-684X;

[2] ORCID : 0000-0002-7578-8715;

[3] ORCID : 0009-0004-8878-9524;

[4] ORCID : 0000-0001-7327-3980;

[5] ORCID : 0000-0002-3829-7132;

[1, 3, 4, 5] Томский национальный исследовательский медицинский центр Российской академии наук, Томск, Российская Федерация

[2] Национальный медицинский исследовательский центр высоких медицинских технологий – Центральный военный клинический госпиталь имени А.А. Вишневского Минобороны России, Красногорск, Российская Федерация

* Корреспондирующий автор (m.a.solovyev[at]mail.ru)

Аннотация

Контроль эффективности назначения Апиксабана в рамках исследования фармакодинамики и фармакокинетики был осуществлен с помощью низкочастотной пьезотромбоэластографии (НПТЭГ) для первого и валидированной методики ВЭЖХ-МС/МС для второго. Полученные данные были сравнены в рамках временного аспекта действия данного НОАК у здоровых добровольцев. Максимальная концентрация назначенного антикоагулянта при однократном приеме в дозировке 5 мг была достигнута на 4-м часу после приема (130 [117;144] нг/мл), при этом резкое увеличение концентрации было достигнуто уже на первом часу наблюдения до 97 [86;105] нг/мл. После достигнутого пика концентрации отмечается планомерное снижение концентрационной активности в крови от 120 [108;130] нг/мл на 6-м, до 97 [88;107] нг/мл на 10-м часу наблюдения, через 84 [75;93] нг/мл на 12-м и до 19 [17;22] нг/мл на 24-м часе. По результатам глобального теста НПТЭГ на 2-х часовой точке мониторинга при его концентрации в пределах 110 [99;121] нг/мл обозначается картина хронометрической и структурной гипокоагуляции. Через 3 часа после приема данного НОАК концентрация препарата достигла 123 [110;135] нг/мл, что на данном временном этапе отразилось в

виде формирования гипокоагуляционного сдвига гемостатического потенциала по данным статистически значимого прироста времени достижения точки «желирования» и снижения константы тромбиновой активности по отношению к таковым, оцененным исходно (p≤0,05). Максимальные проявления гипокоагуляции (статистически значимый прирост времени «желирования» при снижении максимальной амплитуды, константы тромбиновой активности и индекса коагуляционного драйва p≤0,05) выявлены на 4-х часовой точке мониторинга, где определена и максимальная концентрация препарата. По результатам НПТЭГ через 6 часов после приема препарата в крови выявлена умеренная структурная гипокоагуляция, которая к 10-му часу наблюдения, по выраженности проявлений, определяется лишь как тенденция. Через 12 часов отмечается повышение тромбиновой активности и сокращение времени «желирования» по отношению к исходным данным. Полученные результаты позволяют сделать заключение о возможности использования технологии НПТЭГ для мониторинга фармакодинамики Апиксабана в отличие от стандартных методик контроля, при которых результаты эффективности доступны в диапазоне рабочих плазменных концентраций препарата от ~110 нг/мл и выше.

Ключевые слова: низкочастотная пьезотромбоэластография, гемостатический потенциал, противотромботическая терапия, персонификация, апиксабан, НОАК.

Introduction

In recent decades, a number of non-vitamin K antagonist anticoagulant (NOAC) have appeared, an action of which is aimed at the prevention and treatment of thrombotic complications. But prompt diagnosis and monitoring of the effectiveness of NOAC remains a fairly pressing task for practicing physicians [9], [15], [16]. In contrast to numerous instructions for existing NOAC, which stipulate that it is not necessary to monitor the effect of these drugs, but there are instructions for specific or modified laboratory tests to assess the effect of these drugs on the hemostatic system. Of the NOAC used in the clinic, apixaban stands out, the effectiveness of which is recommended to be assessed by a chromogenic test using Rotachrom Heparin, although in practice it has significant laboratory variability [1], [3], [7], [10], [11]. In solving the identified problem of prompt diagnosis of disorders in hemostasis system and monitoring the effectiveness of their correction, a “global” test for integrative assessment of the participation of plasma and cellular components of whole blood in the process of fibrinogenesis was used [5], [6], [13], [17]. The method of low-frequency piezothromboelastography (LFPTEG), which makes it possible to monitor in real time all changes in the viscoelastic properties of native blood, which directly depend on the viability of fibrinogenesis, during its coagulation with a permanent assessment of the hemostasis system [12], [15], [17].

The purpose of the study was to evaluate the possibility of monitoring the anticoagulant effectiveness of 5 mg of Apixaban after a single dose in healthy volunteers and determining its relationship with plasma concentrations of the drug.

Research methods and principles

There were 12 healthy volunteers took part in research, of which 7 men, 5 women, aged from 35 to 45 years, after signing informed consent for the examination. The study was conducted in accordance with the requirements of the Declaration of Helsinki, the study design was approved by the local ethics committee.

Before the start of the study, a catheter was installed in a vein of the forearm for 24 hours to collect blood into 6 ml vacutainers containing K EDTA as an anticoagulant to assess the plasma concentration of the drug. Blood sampling was carried out: initially (10-15 minutes before taking 5 mg of Apixaban "Bristol-Myers Squibb Company", USA and 1, 2, 3, 4, 6, 10, 12 and 24 hours after taking the drug). Blood plasma was separated by centrifugation at 300 rpm for 30 min while cooling, after which it was transferred to a cryovial (the volume of the analytical aliquot was at least 1.5 ml) and immediately frozen on dry ice. Next, the samples were sent to the laboratory to analyze the concentration of the drug. Determination of Apixaban concentrations in samples was carried out by HPLC-MS/MS method validated in accordance with the guidelines [14].

The state of the blood aggregation regulation system was assessed initially, 2, 4, 6 and 12 hours after taking the drug using the LFPTEG method using an ARP-01M Mednord thromboelastograph (Mednord-Technique LLC, Russia). Blood was taken from the vein of the forearm of the free arm without applying a tourniquet in the amount of 0.45 ml of native venous blood. In this case, the interval between taking blood and placing it in the cuvette of the device did not exceed 20 s [17].

The following parameters of the LFPTEG were analyzed: t_1 – reaction period (time in minutes from the start of the study until the minimum amplitude of the LFPTEG was achieved – A_1); t_3 – blood coagulation time (BCT) – point of gelation(PG) in min; t_5 – time to reach the maximum amplitude of the LFPTEG (A_5), ICC – Intensity of contact coagulation, reflecting mainly the suspension stability of blood cells (BCC); ICD – The intensity of the coagulation drive, which characterizes the predominantly proteolytic stage of the third phase of hemocoagulation. TAC – Thrombin activity constant as a universal criterion for assessing the intensity of the proteolytic stage of fibrin formation; MA – Maximum amplitude, characterizing the maximum density of the clot.

Statistical processing of the obtained data was carried out using the IBM SPSS Statistics 22.0 program. To test the null hypothesis, comparisons between the studied independent groups were carried out using the Mann-Whitney test; differences were considered statistically significant at a significance level of $p \le 0.05$. Quantitative indicators are presented in the form Me [LQ; Uq], where Me is the median, LQ (Q25) is the lower quartile, UQ (Q75) is the upper quartile.

Main results

As can be seen from the results obtained, already at the 1st hour of observation, due to high bioavailability and high absorption rate, the concentration of the drug in the blood plasma is determined within the range of 97 [86;105] ng/ml. By the 2nd hour, the concentration of the investigational anticoagulant increases to 110 [99;121] ng/ml, and at the 3rd hour it reaches 123 [110;135] ng/ml. Almost in accordance with the reference data, C_{max} is determined in the 4th hour after taking the drug, reaching ≈ 130 [117;144] ng/ml, with an initial “load” of 5 mg. By the 6th hour of monitoring, the plasma concentration of the drug decreases to 120 [108;130] ng/ml, then, at the 10th hour, to 97 [88;107] ng/ml, and at the 12th to 84 [75;93] ng/ml. After 24 hours in healthy volunteers, the plasma concentration of the drug remains within 19 [17;22] ng/ml.

The results of LFPTEG changes in the hemostatic system at the designated study points are presented in Table 1. Indicators of the hemostatic system in healthy individuals were within normal limits, which is confirmed by LFPTEG data. After some time, or rather 1 hour after administration, the plasma concentration of the test anticoagulant changed to ~97 [86;105] ng/ml. The data obtained could not allow us to judge statistically significant changes in the analyzed characteristics of the LFPTEG. The concentration of apixaban in the blood plasma after 2 hours reaches 110 [99;121] ng/ml, while on LFPTEG a pattern of hypocoagulation is formed, which is statistically significant ($p<0.05$). We achieve the most pronounced hypocoagulation 3 hours after taking the drug, which is statistically significantly confirmed by an increase in the time to reach the "gelation" point and a decrease in the thrombin activity constant in relation to the initial data ($p<0.05$). The plasma concentration of apixaban 4 hours after taking the anticoagulant is ≈ 123 [110;135] ng/ml. At this point, hypocoagulation is observed, which is confirmed by a statistically significant increase in the "gelation" time on LFPTEG ($p <0.05$). The maximum amplitude decreased, as did the thrombin activity constant and the coagulation activity index. Subsequently, moderate structural hypocoagulation persists for up to 6 hours, which is confirmed by a statistically significant decrease in CBC and MA ($p <0.05$). And by the 10-hour observation point, the severity of manifestations is noted as a trend. Already by 12 hours, a compensatory increase in thrombin activity and a decrease in the "gelation" time ($p < 0.05$) in relation to the initial data are observed throughout the entire osmium.

Table 1 - The values of the measured characteristics of NPTEG by observation "points" in healthy volunteers after a single dose of 5 mg of Apixaban

DOI: https://doi.org/10.60797/IRJ.2024.144.84.1

Indicators	originally	2 hours	3 hours	4 hours	6 hours	10 hours	12 hours
t_1 (min.)	1[0,8;1,8]	1,3 [1,1;2,0]	1,8 [1,3;2,1]*	1,6 [1,1;1,9] *	1,2 [1,5;3,1]	1,1 [0,8;1,7]	0,9 [0,7;2,0]
ICC (r.u.)	16[11;22]	13 [11;18]	14 [11;21]	18 [15;22]	15 [10;19]	17 [11;20]	16 [14;24]
t_3 (min.)	8[7;10]	11 [10;15] *	13 [12;15] *	15[14;17] *	15 [14;16] *	10 [9;12]	6 [5;7]#
TAC (r.u.)	30[25;34]	26 [25;34]	23 [20;24] *	15 [12;18] *	20 [17;23] *	27 [24;32]	35 [29;40] #
ICD (r.u.)	32[30;35]	29 [27;32]	29 [26;33]	22 [19;28] *	30 [28;35]	30 [27;34]	31[27;35]
t_5 (min.)	31[29;33]	40 [30;48] *	37[31;45]	46 [41;50] *	37 [30;48]	34 [30;48]	28 [25;34]
MA (r.u.)	560[490;610]	530 [500;630]	550 [490;600]	430 [400;530] *	450 [420;500] *	550[480;600]	590 [500;650]

*Note: * - statistically significant differences from the initial values (p≤0.05 – changes in the hypocoagulation plan); # - statistically significant differences from the initial values (p≤0.05 – changes in the hypercoagulation plan)*

Conclusion

The results obtained allow us to conclude that it is possible and necessary to use LFPTEG technology in real time to monitor the pharmacodynamics of apixaban, in contrast to standard control methods that operate in the range of working concentrations of the drug in plasma from ~110 ng/ml and above when assessing the effectiveness of anticoagulant therapy.

Финансирование

Grant No. 22-15-20041, https://rscf.ru/project/22.03.2022.

Конфликт интересов

Не указан.

Рецензия

Все статьи проходят рецензирование. Но рецензент или автор статьи предпочли не публиковать рецензию к этой статье в открытом доступе. Рецензия может быть предоставлена компетентным органам по запросу.

Funding

Грант No. 22-15-20041, https://rscf.ru/project/22.03.2022.

Conflict of Interest

None declared.

Review

All articles are peer-reviewed. But the reviewer or the author of the article chose not to publish a review of this article in the public domain. The review can be provided to the competent authorities upon request.

Список литературы / References

1. Дементьева И.И. Технологии оказания медицинской помощи в клинике неотложной помощи / И.И. Дементьева, Ю.А. Морозов, М.А. Чарная и др. // Клин. лаборатория диагностика. — 2013. — 7. — с. 5-10.

2. Gouin-Thibault I. Assessment of apixaban plasma levels by laboratory tests: suitability of three anti-Xa assays / I. Gouin-Thibault, C. Flaujac, X. Delavenne et al. // Thromb. Haemost. — 2014. — 111(02). — p. 240-248. — DOI: 10.1160/TH13-06-0470.

3. Heidbuchel H. European Heart Rhythm Association. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation / H. Heidbuchel, P. Verhamme, M. Alings et al. // Europace. — 2013. — 15. — p. 625–651.

4. Миронов А.Н. Руководство по экспертизе лекарственных средств / А.Н. Миронов. — Москва: Гриф и К, 2013. — 328 с.

5. Момот А.П. Динамика показателей гемостаза при физиологической беременности и после родов / А.П. Момот, Н.А. Семёнова, Д.Е. Белозёров и др. // Журнал расстройств, связанных с переливанием крови. — 2016. — 3. — с. 5.

6. Ревишвили А.Ш. Особенности оказания неотложной и неотложной медицинской помощи пациентам, получающим прямые пероральные антикоагулянты. Консенсусный документ междисциплинарной группы экспертов / А.Ш. Ревишвили, Е.В. Шляхто, М.Н. Замятин // Вестник аритмологии. — 2018. — 92. — с. 59-72. — DOI: 10.25760/VA-2018-92-59-72.

7. Ruff C.T. Association between edoxaban dose, concentration, anti-Factor Xa activity, and outcomes: an analysis of data from the randomised, double-blind ENGAGE AF-TIMI 48 trial / C.T. Ruff, R.P. Giugliano, E. Braunwald et al. // The Lancet. — 2015. — 385(9984). — p. 2288-2295.

8. Sanna T. CRYSTAL AF Investigators. Cryptogenic stroke and underlying atrial fibrillation / T. Sanna, H.C. Diener , R.S. Passman et al. // N Engl J Med. — 2014. — 370. — p. 2478–2486. — DOI: 10.1056/NEJMoa1313600.

9. Соловьёв М.А. Опыт диагностики и мониторинга критических нарушений гемостаза / М.А. Соловьёв, И.И. Тютрин, В.В. Удут и др. // Мед.-биол. и социально-психол. проблема безопасности в чрезвычайных ситуациях. — 2013. — 4. — с. 55-60.

10. Solovyev M.A. Global Tests Evaluating the Functional Condition of Hemostasis / M.A. Solovyev, I.I. Tutrin, V.V. Udut et al. // Clin Exp Pharmacol. — 2015. — 5. — p. 178. — DOI: 10.4172/2161-1459.1000178.

11. Сулимов В.А. Антикоагулянтная терапия в реальной клинической практике: данные ретроспективного поперечного исследования / В.А. Сулимов, Д.А. Напалков, А.А. Соколова и др. // Рац. фармакология в кард.. — 2015. — 11 (2). — с. 116-123.

12. Титаева Е.В. Хромогенный анти-Ха тест: соотношение единиц активности гепарина и концентрации апиксабана и ривароксабана / Е.В. Титаева, А.Б. Добровольский // Атеротромбоз. — 2020. — 2. — с. 96-104. — DOI: 10.21518/2307-1109-2020-2-96-104.

13. Тютрин И.И. Новая технология оценки фармакодинамики антиагрегантов / И.И. Тютрин, В.Ф. Клименкова, В.В. Удут // Фармакол.. — 2014. — 77(2). — с. 21-25. — DOI: 10.30906/0869-2092-2017-80-11-10-17.

14. Тютрин И.И. Низкочастотная пьезотромбоэластография цельной крови: алгоритмы диагностики и коррекции гемостазиологических нарушений / И.И. Тютрин, В.В. Удут — Томск, 2016. — 170 с.

15. Удут В.В. Технология низкочастотной пьезоэлектрической тромбоэластографии для мониторинга антитромботической терапии / В.В. Удут, И.И. Тютрин, М.А. Соловьёв и др. // Клиническая и экспериментальная фармакология. — 2017. — 11. — с. 10-17. — DOI: 10.30906/0869-2092-2017-80-11-10-17.

16. Удут В.В. Технология низкочастотной пьезотромбоэластографии в оценке гемостатического потенциала / В.В. Удут, И.И. Тютрин, Л.Ю. Кольцовская // Вестник новых медицинских технологий. — 2016. — 4. — с. 104-113. — DOI: 10.12737/22220.

17. Udut V.V. Global Tests in Evaluation of the Function of Pro-and Anticoagulant Systems: Present and Future / V.V. Udut, I.I. Tyutrin, M.A Solov’ev et al. // Bull Exp Biol Med. — 2015. — 159. — p. 205-208. — DOI: 10.1007/s10517-015-2923-8.

Список литературы на английском языке / References in English

1. Dementyeva I.I. Tehnologii okazanija meditsinskoj pomoschi v klinike neotlozhnoj pomoschi [Point of care technologies in the emergency clinic] / I.I. Dementyeva, Yu.A. Morozov, M.A. Charnaya et al. // Wedge. lab. diag. — 2013. — 7. — p. 5-10. [in Russian]

2. Gouin-Thibault I. Assessment of apixaban plasma levels by laboratory tests: suitability of three anti-Xa assays / I. Gouin-Thibault, C. Flaujac, X. Delavenne et al. // Thromb. Haemost. — 2014. — 111(02). — p. 240-248. — DOI: 10.1160/TH13-06-0470.

3. Heidbuchel H. European Heart Rhythm Association. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation / H. Heidbuchel, P. Verhamme, M. Alings et al. // Europace. — 2013. — 15. — p. 625–651.

4. Mironov A.N. Rukovodstvo po ekspertize lekarstvennyh sredstv [Guidelines for the examination of medicinal products] / A.N. Mironov — Moscow: Grif i K, 2013. — 328 p. [in Russian]

5. Momot A.P. Dinamika pokazatelej gemostaza pri fiziologicheskoj beremennosti i posle rodov [The dynamics of the hemostatic parameters in physiological pregnancy and after delivery] / A.P. Momot, N.A. Semenova, D.E. Belozerov et al. // J Hematol Blood Transfus Disord. — 2016. — 3. — p. 5. [in Russian]

6. Revishvili A.Sh. Osobennosti okazanija neotlozhnoj i neotlozhnoj meditsinskoj pomoschi patsientam, poluchajuschim prjamye peroral'nye antikoaguljanty. Konsensusnyj dokument mezhdistsiplinarnoj gruppy ekspertov [Features of providing emergency and emergency medical care to patients receiving direct oral anticoagulants. Consensus document of an interdisciplinary group of experts] / A.Sh. Revishvili, E.V. Shlyakhto, M.N. Zamyatin // Bulletin of Arrhythmology. — 2018. — 92. — p. 59-72. — DOI: 10.25760/VA-2018-92-59-72. [in Russian]

7. Ruff C.T. Association between edoxaban dose, concentration, anti-Factor Xa activity, and outcomes: an analysis of data from the randomised, double-blind ENGAGE AF-TIMI 48 trial / C.T. Ruff, R.P. Giugliano, E. Braunwald et al. // The Lancet. — 2015. — 385(9984). — p. 2288-2295.

8. Sanna T. CRYSTAL AF Investigators. Cryptogenic stroke and underlying atrial fibrillation / T. Sanna, H.C. Diener , R.S. Passman et al. // N Engl J Med. — 2014. — 370. — p. 2478–2486. — DOI: 10.1056/NEJMoa1313600.

9. Solovev M.A. Opyt diagnostiki i monitoringa kriticheskih narushenij gemostaza. [Experience in diagnosing and monitoring critical hemostasis disorders] / M.A. Solovev, I.I. Tyutrin, V.V. Udut et al. // Med.-biol. and social-psychol. problem safety in emergency situations. — 2013. — 4. — p. 55-60. [in Russian]

10. Solovyev M.A. Global Tests Evaluating the Functional Condition of Hemostasis / M.A. Solovyev, I.I. Tutrin, V.V. Udut et al. // Clin Exp Pharmacol. — 2015. — 5. — p. 178. — DOI: 10.4172/2161-1459.1000178.

11. Sulimov V.A. Antikoaguljantnaja terapija v real'noj klinicheskoj praktike: dannye retrospektivnogo poperechnogo issledovanija [Anticoagulant therapy in real clinical practice: data from a retrospective cross-sectional study] / V.A. Sulimov, D.A. Napalkov, A.A. Sokolova et al. // Rat. pharm. in card. — 2015. — 11 (2). — p. 116-123. [in Russian]

12. Titaeva E.V. Hromogennyj anti-Ha test: sootnoshenie edinits aktivnosti geparina i kontsentratsii apiksabana i rivaroksabana [Chromogenic anti-Xa test: the ratio between heparin activity units and concentration of apixaban and rivaroxaban] / E.V. Titaeva, A.B. Dobrovolsky // Atherothrombosis. — 2020. — 2. — p. 96-104. — DOI: 10.21518/2307-1109-2020-2-96-104. [in Russian]

13. Tyutrin I.I. Novaja tehnologija otsenki farmakodinamiki antiagregantov [New technology for assessing the pharmacodynamics of antiplatelet agents] / I.I. Tyutrin, V.F. Klimenkova, V.V. Udut // Pharmacol. — 2014. — 77(2). — p. 21-25. — DOI: 10.30906/0869-2092-2017-80-11-10-17. [in Russian]

14. Tyutrin I.I. Nizkochastotnaja p'ezotromboelastografija tsel'noj krovi: algoritmy diagnostiki i korrektsii gemostaziologicheskih narushenij [Low-frequency piezothromboelastography of whole blood: algorithms for diagnosis and correction of hemostasiological disorders] / I.I. Tyutrin, V.V. Udut — Tomsk, 2016. — 170 p. [in Russian]

15. Udut V.V. Tehnologija nizkochastotnoj p'ezoelektricheskoj tromboelastografii dlja monitoringa antitromboticheskoj terapii [Low-frequency piezoelectric thromboelastography technology for antithrombotic therapy monitoring] / V.V. Udut, I.I. Tutrin, M.A. Solovyev et al. // Clin. Exp. Pharmacol. — 2017. — 11. — p. 10-17. — DOI: 10.30906/0869-2092-2017-80-11-10-17. [in Russian]

16. Udut V.V. Tehnologija nizkochastotnoj p'ezotromboelastografii v otsenke gemostaticheskogo potentsiala [Low-frequency piezothromboelastography technology in assessing hemostatic potential] / V.V. Udut, I.I. Tyutrin, L.Yu. Kotlovskaya // Bulletin of New Medical Technologies. — 2016. — 4. — p. 104-113. — DOI: 10.12737/22220. [in Russian]

17. Udut V.V. Global Tests in Evaluation of the Function of Pro-and Anticoagulant Systems: Present and Future / V.V. Udut, I.I. Tyutrin, M.A Solov’ev et al. // Bull Exp Biol Med. — 2015. — 159. — p. 205-208. — DOI: 10.1007/s10517-015-2923-8.