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POSSIBILITIES FOR MONITORING THE PHARMACODYNAMICS OF DABITAGRAN ETEXILATE

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The sensitivity and prognostic significance of laboratory tests and methods for assessing pharmacodynamics in relation to the system of regulation of the aggregate state of blood after a single dose of dabigatran etexilate at a dosage of 150 mg were investigated. Determination of the functional state of the hemostatic potential of native blood was carried out using thromboelastography (before and after 2, 4, 12 hours after taking the drug) and low-frequency piezothromboelastography (before taking the drug and after 2, 4, 8, 12 and 24 hours after taking the drug). In parallel with the study of changes in the viscoelastic properties of native blood, the dynamics of the activated partial thromboplastin time was monitored (before taking the drug and 2, 4 and 12 hours after taking the drug).

According to the results of LFPTEG, the maximum severity of the direct pharmacodynamic effect of dabigatran etexilate was recorded 4 hours after taking the drug (which was reflected by a pronounced decrease in the efficiency of the proteolytic stage of fibrinogenesis) with the return of the activity of the proteolytic stage of fibrinogenesis to the initial level at 8 hours with the retention of residual antithrombotic activity up to 12 hours.

The use of thromboelastography was limited to a 4-hour interval, while the APTT test was limited to 2 hours from the moment of taking the drug, after which the level of indicators returned to the initial value.

Keywords: system of regulation of the aggregate state of blood, dabigatran etexilate, hemocoagulation, hemostatic potential, whole blood, global tests, low-frequency piezothromboelastography.

Introduction. To date, anti-thrombotic therapy has a wide range of anticoagulant agents to offer, including a group of direct oral anticoagulants (DOA), associated with new opportunities for pharmacological thrombosis prevention. Distinctive features of this group of drugs are oral administration, targeted action (factor Xa: apixaban and rivaroxaban, factor IIa: dabigatran), and absence of the need for laboratory control of therapy — a feature that most clinicians would appreciate [17]. Dabigatran is the first DOA group drug approved for use in clinical practice. Its efficacy and safety have been confirmed in several studies [15], specifically, RE-MODEL (2007), RE-NOVATE (2007), RELY (2009), RE-COVER (2009), REMEDY (2013), RE-SONATE (2013), RE-ALIGN (2013), RE-DUAL PCI (2017), RESPECT ESUS (2019), RESPECT CVT (2019).

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However, the actual clinical safety and efficacy of the drug observed in the course of routine practice differ from the data obtained in the phase III of clinical trials [2,13], which creates presuppositions for ethical contradictions among practitioners. For instance, the RE-CIRCUIT study (2017) designed to compare the efficacy/safety of dabigatran and warfarin in patients with mechanical heart valves revealed an increased incidence of thromboembolism and hemorrhagic complications in patients receiving dabigatran [8], which was the reason for the early termination of the study. As demonstrated in the work [11], the use of dabigatran, compared to warfarin, is associated with an increased risk of major bleedings, a higher risk of gastrointestinal bleeding, but a lower risk of intracranial hemorrhages. There has also been a number of reports of severe/fatal bleeding in elderly and senile patients [5, 6, 19]. In addition, hypercoagulation that develops after discontinuation of administering dabigatran may also be a significant concern [14]. Thus, lack of laboratory control of dabigatran therapy is quite a significant problem [7].

Currently, dabigatran is recommended as a first-line drug for the treatment of venous thromboembolic complications in patients with non-valvular atrial fibrillation, with advised twice-daily intake of 150 mg [18]. The recommendations for monitoring the efficacy and safety are reduced to the analysis of clinical data (examination findings, medical history) using specialised scales (HAS-BLED, CHA2DS2-VASc, etc.). This approach lacks any objective criteria for the assessment of the functional state of the hemostatic potential – an integrative component of the full-cycle hemocoagulation, which ensures the necessary blood fluidity and restricts extravasation of blood components in cases of disruption of the vascular wall integrity or any damage to it [1,3].

A number of laboratory tests have been proposed to monitor the efficacy/safety of dabigatran, including activated partial thromboplastin time (APTT), ecarin blood clotting time (ECT) and diluted thrombin time (Hemoclot) [4]. All these tests have similar disadvantages: they analyse only a certain "cluster" of hemocoagulation but are not implemented in routine clinical practice (ECT, Hemoclot) and have a low level of standardisation [9, 10, 16].

Dabigatran is known to have an effect not only on free thrombin (and, as a result, on the plasma component of hemostasis), but also on thrombin associated with the formation of fibrin clots, and on the thrombin-induced platelet activation [12], reducing the level of their participation in thrombogenesis. In addition to the weakened functional responses of platelets mediated through PARs receptors, the cellular component is also affected by other components of anti-thrombotic therapy (two- or three-component therapy) prescribed together with dabigatran. This is what identifies the need not only to assess the "peak" effect of dabigatran, determined by integrative hemostasis tests, but also to assess the effect of a combination of anti-thrombotic agents on the hemostatic potential, in general, taking into account

the cellular component of hemostasis.

Thus, the problem discussed above entails the need to develop an algorithm for evaluating the efficacy/safety of dabigatran which would meet the following criteria: (I) it could be performed using native blood; (II) it would provide information on all components of fibrinogenesis (starting from initiation/amplification to the formation of cross-linked fibrin and possible clot lysis), and (iii) it could be carried out in the "Point-of-care testing" mode.

To date, the integral characteristic of the hemostatic potential of native blood can only be obtained using such "global" hemostasis system tests as the rotational (TEG, ROTEM) and vibration (LFPTEG) viscometry. These methods determine changes in the physical state of blood, however they show a fundamental difference when it comes to the comparison of the informative value of the data obtained – the LFPTEG method registers changes in blood viscosity at the initial stages of fibrinogenesis, in the time interval that is identified as the "lag-time" in the TEG [1,3]. This allows us to analyse the intensity of hemocoagulation during the initiation/amplification phases and to determine the activity of the proteolytic stage of fibrinogenesis, whereas the TEG and ROTEM methods provide information only on the post-coagulation phase of fibrinogenesis.

The objective of this study was a comparative assessment of the informative value of global tests of the hemostasis system in relation to the control of the efficacy of dabigatran etexilate.

Table 1

Volunteer selection criteria

Criteria	Approved	Not approved
Male sex	+	–
Age from 18 to 55	+	–
Body mass index: 18.5 – 24.99	+	–
Taking antiplatelet, anticoagulant, fibrinolytic, antihypertensive or other drugs affecting the hemostatic system.	–	+
Suffering from diseases in the acute stage and/or exacerbation of chronic diseases	–	+
Suffering from diseases that affect the hemostatic system	–	+
Thrombotic complications in the medical history	–	+

Materials and methods. The study was conducted at the clinic of the E. D. Goldberg Research Institute of Pharmacology and Regenerative Medicine. Thirty healthy male volunteers participated in the study after signing a voluntary informed consent. The criteria for the volunteer selection for the study is presented in Table 1.

Apart from medical history check (identification of complaints), the screening stage included general and biochemical blood tests. The general blood test was performed on whole stabilized venous blood using an ABX Micros ES 60 analyzer (HORIBA ABX SAS, France). The biochemical blood test was performed on citrate plasma (alkaline phosphatase and total bilirubin were checked on serum) using an automatic biochemical analyzer Erba Mannheim XL 200 (Erba Lachema, Czech Republic). At the end of the screening, provided that the selection criteria were met, the participants' hemostatic potential was monitored over time after a single 150 mg dose of dabigatran etexilate (Pradaxa, Boehringer Ingelheim International GmbH, Germany).

APTT was determined on platelet-poor plasma using a 4-channel semi-automatic coagulometer Amelung KC 4 delta (TRINITY Biotech, Ireland) 2, 4, and 12 hours after the drug intake.

TEG was performed on native venous blood taken without a tourniquet, using a TEG 5000 thromboelastograph (Haemoscope Corporation, USA). The pharmacodynamics of dabigatran were monitored 2 and 12 hours after the drug intake; the following TEG parameters were evaluated:

- R (min) – the time from the start

Table 2

Estimated LFPTEG parameters

Indicator	Meaning
ICC, per units. Intensity of contact coagulation	Displays the aggregation activity of blood corpuscles
ICD, per units. Intensity of coagulation drive	Displays the proteolytic stage and the beginning of the polymerization stage of the third phase of blood clotting
CTA, per units. Constant of thrombin activity	Criterion for assessing the intensity of the proteolytic stage of fibrinogenesis
ICP, per units. Intensity of clot polymerization	Displays the intensity of the polymerization stage
MA, per units. Maximum amplitude of the clot	Characteristics of the maximum density of the clot due to the activity of the blood corpuscles and the qualitative and quantitative characteristics of the cross-linked fibrin after the completion of polymerization and the retraction process
ITC, per units. Intensity of total clotting	General evaluation of the intensity of cross-linked fibrin formation
IRCL, per units. Intensity of the retraction and clot lysis	Evaluation of the lytic activity in the studied blood sample
TAAF, per units. Total anticoagulation activity factor	Displays the total anticoagulation activity in the aliquot
t1, min.	Characterizes the suspension stability of the blood
t3, min.	Blood gelation time
t5, min.	Time to reach the maximum density (retraction) of the clot

of the test to the detection of signs of thrombosis (when the signal reaches an amplitude of 2 mm).

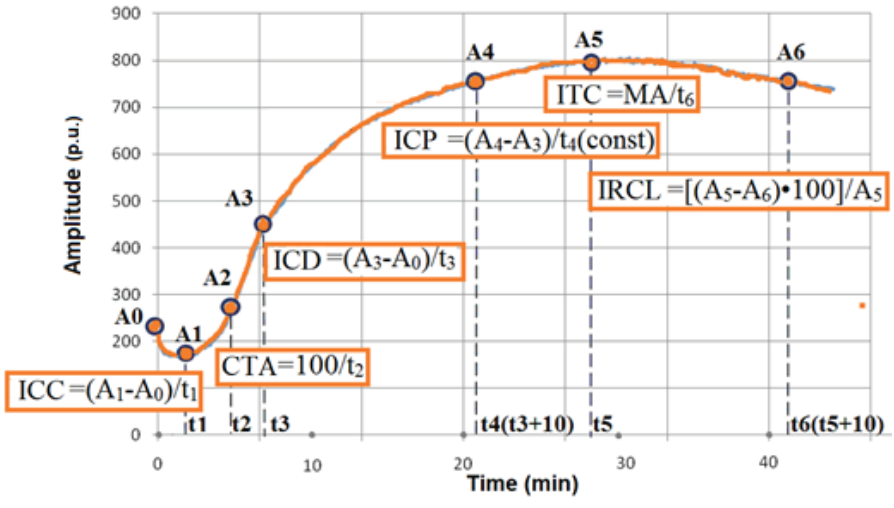
- Angle α (°) – the angle constructed tangentially to the TEG from the point of the beginning of the clot formation, which reflects the rate of growth of the fibrin formation and its structure (increase in the clot strength).
- K (min) – the time of initial thrombosis (reaching the signal amplitude of 20 mm).
- MA, mm – the maximum amplitude of the curve that characterizes the maximum dynamic properties of the connection between fibrin and platelets and shows the content of fibrinogen and the maximum clot strength.

The hemostatic potential was determined using the LFPTEG method on native venous blood collected from the vein in the bend of the elbow joint without a tourniquet, using the ARP-01M Mednord thromboelastograph (Registration certificate of Federal service for surveillance in healthcare № 2010/09767). The estimated parameters of the piezothromboelastogram are given in Table 2; the approximation of the estimated parameters to the piezothromboelastogram curve is shown in Figure 1.

Statistical processing of the obtained data was carried out using the IBM SPSS Statistics 22.0 programme. To check the null hypothesis, the comparison of the independent study groups was conducted using the Mann-Whitney test; the differences were recognized as statistically valid at a significance level of $p < 0.05$. Quantitative indicators are presented as Me [LQ; Uq], where Me is the median, LQ (Q25) is the lower quartile, and UQ (Q75) is the upper quartile.

Results of the research. Dabigatran showed the maximum anticoagulant effect in 2-4 hours after the drug intake (Tables 3-4).

The statistically significant differences in the APTT index compared to the baseline level were recorded only at the start of the second hour after dabigatran intake (an increase of 1.38 times, p = 0.001). TEG demonstrated quite a significant period of time: the second hour showed lengthening of the time of the beginning of clot formation (R increase by 1.11 times, p = 0.009), reduced growth rate of the fibrin formation (alpha angle value decrease by 1.08 times, p = 0.001) and a decrease of the maximum density of the clot (MA decrease by 1.1 times, p=0.001). The changes in level of indicators that are characteristic of structural hypocoagulation persisted for 4 hours: a decrease in the intensity of fibrinogenesis (alpha angle value decrease by 1.05 times, p=0.001) and a decrease in the maximum clot density (MA decrease by 1.09 times, p=0.001) were recorded. In 12 hours after dabigatran intake, no statistically significant differences between the parameters of the thromboelastogram and the initial parameters were registered.



Piezothromboelastogram curve specifying the parameters

LFPTEG was the most informative of all the used methods (Table 4)

According to the results of the LFPTEG, the effect of dabigatran was registered on the 2nd hour after the drug intake, and the maximum effect was reached after 4 hours.

In a two-hour interval after the dabigatran intake, the hemostatic potential was characterized by a decrease in the overall intensity of hemocoagulation (ITC decrease by 1.22 times, p = 0.016). Moderate anticoagulation occurred due to an increase in the suspension stability (t1 increase by 3.07 times, p = 0.001), reduction of the intensity of proteolytic stage of clot formation (CTA and ICD levels decreased by 2.57 times (p = 0.016) and 1.9 times (p = 0.002), respectively), as well as an increase in the time of blood gelation (t3 increase by 3.07 times, p = 0,018). In addition, a decrease in anticoagulant activity against the background of chronometric hypocoagulation was registered (TAAF decrease by 1.82 times, p = 0.002).

The "peak" action of dabigatran is characterised by a general decrease in the intensity of coagulation (ITC decrease by 1.22 times, p = 0.01): increased suspension stability of the blood (t1 increase by 3.15 times, p = 0.001), decreased intensity of proteolytic stage fibrinogenesis (CTA and ICD levels decreased by 3.33 times (p = 0.003) and 2.01 times (p = 0.001) respectively), and an increase in the time of blood gelation (t3 increase by 2.05 times, p = 0.003) compared to the baseline level. Against the background of a general decrease in the intensity of fibrinogenesis, a decrease in the intensity of the anticoagulant potential (TAAF decrease by 1.82 times, p = 0.001) was also registered with regard to the baseline level.

In 8 hours after the drug intake, a number of indicators returned to the initial level (CTA and t3). At the same time, a decrease in the level of the t1 indicator was recorded simultaneously with an increase in the levels of ITC and TAAF indicators, which demonstrated a shift in the hemostatic potential towards normal coagulation, which returned to the previous level of hypocoagulation in 12 hours.

The hypocoagulation state of the hemostatic potential remained for up to 12 hours after the drug intake (ITC decrease by 1.2 times, p = 0.024): suspension stability of the blood remained (t1 increase by 1.66 times, p = 0.015), and the intensity of fibrinogen proteolysis decreased (ICD decrease by 1.48, p = 0.035). At the 24th hour of the study, the HP of the healthy volunteers was characterized by a normal coagulation state comparable to the baseline level. However, at the final point, all volunteers registered an isolated increase in the aggregation activity of the blood corpuscles, which was evidences by an increase in ICC value by 1.71 times (p = 0.029) compared to the initial value. The change of this parameter over time shows an isolated increase in the aggregation activity of the blood corpuscles, observed after the end of the drug effect.

Conclusion. This article presents the results of comparative monitoring of the pharmacodynamics of dabigatran etexilate after a single intake of 150 mg of

the drug by healthy male volunteers with a local APTT hemostasis test, as well as global tests - TEG and LFPTEG.

The APTT test showed informative value only at the "peak" of the dabigatran action (2 hours after the intake), since the blood test sample taken in 4 hours after the intake did not show any statistically significant differences if compared to the baseline level.

The possibility of a longer monitoring of the pharmacodynamics of dabigatran was identified in a study using native blood.

Thromboelastography performed on native blood for the purpose of monitoring the pharmacodynamics of dabigatran proved not to be informative enough – a decrease in the rate of formation (R and α angle indicators), gelation and density of the fibrin-platelet structure (MA indicator) was observed against the background of the maximum effect of dabigatran. However, in 12 hours after dabigatran intake, no statistically significant differences between the parameters of the thromboelastogram and the initial parameters were registered. Thus, the method of thromboelastography was not informative enough to be used for dynamic monitoring of the hemostatic potential, since for the most part it displayed only structural hypocoagulation observed after dabigatran intake and showed practically no chronometric hypocoagulation.

And vice version, the LFPTEG method, which demonstrated the largest time range of the possibility of registering the action of dabigatran, predominantly recorded changes in parameters reflecting the chronometric hypocoagulation of the initial stages, a decrease in the intensity of the proteolytic stage of fibrinogenesis, and an increase in the time of blood gelation. In response to a decrease in the intensity of clot formation, a decrease in the total anticoagulant activity of the blood was recorded. In contrast to the data obtained by the TEG method, according to the results of the LPTEG over 24 hours, there was no decrease in the intensity of fibrin polymerization, the time of formation of cross-linked fibrin and the maximum polymerization stage of fibrinogenesis. Also, the NPTEG method in all study participants at the 24th hour after taking dabigatran showed an isolated increase in the aggregation activity of blood corpuscles. Given the absence of changes in the dynamics of aggregation of blood corpuscles during induced hypocoagulation and its intensification after the end of the action of the anticoagulant, it becomes necessary to conduct further studies with a closer study of platelet aggregation.

Table 3

Dynamic monitoring of activated partial thromboplastin time and thromboelastography in healthy volunteers before and after dabigatran intake

Indicator		Background	In 2 hours	In 4 hours	In 12 hours
APTT		36.0 [35.5; 38.5]	50.0 [47.0; 52.0]*	37.0 [35.0; 42.0]	38.0 [36.5; 42.5]
TEG	R	13.5 [13.0; 15.5]	15.0 [14.5; 16.5]*	13.5 [13.0; 14.5]	13.0 [13.0; 14.5]
	Angle α	49.0 [47.5; 50.0]	45.0 [44.0; 45.0] *	46.5 [45.5; 47.0]*	48.0 [47.0; 49.5]
	K	6.5 [5.0; 7.0]	7.0 [6.5; 7.0]	6.5 [5.5; 6.5]	6.0 [5.0; 6.5]
	MA	51.0 [50.0; 60.0]	46.0 [45.0; 46.5] *	46.5 [45.0; 47.0]*	50.0 [49.0; 56.0]

Notes to Table 3: * - statistically significant differences in comparison with the background level of the indicator, $p \leq 0.05$

Table 4

Dynamic monitoring of low-frequency piezothromboelastography in healthy volunteers before and after dabigatran intake

Indicator	Background	In 2 hours	In 4 hours	In 8 hours	In 12 hours	In 24 hours
T1, min	1.30 [1.15; 1.65]	4.00 [3.90; 4.10]*	4.10 [4.00; 4.20] *	2.20 [2.00; 3.80] *	2.40 [2.20; 2.45]*	1.30 [1.15; 1.35]
ICC, per units.	10.83 [8.00; 15.78]	12.20 [11.90; 12.50]	11.90 [10.47; 12.50]	13.89 [12.11; 18.18]	5.42 [3.71; 15.21]	18.57 [16.98; 24.29]*
CTA, per units.	47.62 [29.76; 69.05]	18.52 [16.39; 19.23] *	14.29 [12.66; 14.93] *	28.57 [24.39; 33.33]	33.33 [33.33; 33.91]	33.33 [32.29; 33.91]
T3, min	7.80 [5.00; 10.40]	12.80 [12.00; 14.10] *	16.00 [15.50; 17.90] *	9.80 [9.20; 12.00]	10.20 [9.10; 12.10]	7.20 [6.60; 7.35]
ICD, per units.	38.63 [27.37; 51.06]	20.31 [20.00; 21.28] *	19.21 [17.14; 19.35] *	25.59 [20.17; 26.12] *	25.98 [25.31; 26.74] *	38.61 [38.31; 41.81]
ICP, per units.	14.60 [12.15; 16.25]	15.00 [13.50; 17.50]	13.00 [12.00; 13.50]	14.00 [12.90; 14.00]	13.80 [11.90; 15.90]	16.30 [15.65; 16.50]
T5, min	37.60 [34.25; 45.90]	46.00 [45.00; 47.00]	45.80 [45.00; 46.00]	44.00 [42.00; 46.00]	45.50 [45.00; 45.75]	37.20 [36.60; 37.85]
MA, per units.	522.0 [493.5; 557.5]	500.0 [480.0; 550.0]	500.0 [490.0; 520.0]	498.0 [490.0; 525.0]	515.0 [501.5; 545.0]	486.0 [483.0; 500.5]
ITC, per units.	13.66 [12.50; 14.85]	11.11 [10.43; 11.70] *	11.36 [10.70; 11.56] *	11.67 [11.62; 11.93] *	11.32 [11.15; 11.91] *	13.33 [12.98; 13.59]
IRCL, %	0.38 [0.32; 0.94]	0.62 [0.46; 1.82]	0.65 [0.50; 1.33]	0.67 [0.31; 0.92]	1.21 [0.85; 1.45]	0.67 [0.34; 1.73]
TAAF, per units.	2.59 [2.21; 3.30]	1.42 [1.16; 1.81] *	1.42 [1.24; 1.51] *	2.11 [1.73; 2.48] *	1.88 [1.71; 2.17] *	2.37 [2.33; 2.69]

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