Features of Pharmacodynamics of the Anticoagulant Dabigatran in Secondary Thrombophilia

Gaisa T. Kairov, PhD[1], Maksim A. Solovev, PhD[2,3], Larisa Y. Kotlovskaya[2,3], and Vladimir V. Udut, PhD[2,3]

Abstract

One of the crucial risk factors for development of severe postthrombotic disease (PTD) is the recurrence of deep vein thrombosis (DVT). New opportunities for pharmacological thromboprophylaxis of secondary thrombophilia were associated with the direct thrombin inhibitor—Dabigatran (Pradaxa; Boehringer Ingelheim, Germany). We aimed to investigate the daily pharmacodynamics of dabigatran in healthy volunteers and patients with PTD. Treatment with dabigatran in patients with PTD having chronic chronometric hypercoagulation and structural hypocoagulation before the administration of the drug is fraught with excessive anticoagulation and a high risk of clinically significant bleeding. In patients with PTD with detected chronometric and structural hypercoagulability before taking a direct thrombin inhibitor, treatment with dabigatran is fraught with possible inadequate anticoagulation and a high risk of clinically significant relapses of thromboses. According to our data, markers of risk of hemorrhagic complications under Dabigatran are the thromboelastography indicators lying within the reference values of the healthy before the administration of the drug: fibrin–platelet clot formation, maximum amplitude of TEG; total lytic activity of blood, and thrombodynamic potential index . Monitoring the effects of the targeted anticoagulant demonstrated the need for correction of dosage and discrete use of the drug in prevention and treatment for thrombohemorrhagic complications in this category of patients. The results of the study prove the efficiency of the therapy with dabigatran and "behavior" of hemostatic potential in patients being taken into account and controlled. Therapy may be long term but requires dynamic monitoring of patients with timely dose adjustment to achieve and maintain the target level of hemostatic potential.

Keywords

dabigatran, pharmacodynamics, hemostatic potential, post-thrombotic disease, thromboelastography, bleeding

Introduction

The most common diseases of the vascular system are venous thromboembolic complications (VTECs) that combine deep vein thrombosis (DVT) and pulmonary embolism (PE). In the general population, 1 to 2 cases of VTEC are registered annually per 1000 people.[1] In the structure of causes of death from cardiovascular diseases, fatal PE occupies the third place after myocardial infarction and stroke.[2] After the initial episode of DVT, within 2 years, 20% to 50% of patients develop postthrombotic disease (PTD), and the relapse rate of VTEC within the first 5 years reaches 25%.[3,4] Postthrombotic disease is a chronic obstruction of venous outflow from the lower extremities that develops after a DVT has been transferred. There are 2 variants of the disease (edematous and edematous varicose forms) and 3 stages of PTD (transient edema, "severe leg syndrome," and persistent edema), trophic disorders (skin pigmentation disorders, eczema, and lipodermatosclerosis), and

trophic ulcers. In the early stages, patients complain of pain, a feeling of bursting, and heaviness in the affected leg when walking or standing. When lying, giving the limb an elevated position, the symptoms quickly decrease. A characteristic sign

[1] Department of Anaesthesiology and Reanimatology, Siberian State Medical University, Tomsk, Russia
[2] Laboratory of Physiology, Molecular and Clinical Pharmacology, Goldberg Research Institute of Pharmacology and Regenerative Medicine, Tomsk National Research Medical Center of the Russian Academy of Science, Tomsk, Russia
[3] Laboratory for Modelling of Physical Processes in Biology and Medicine, National Research Tomsk State University, Tomsk, Russia

Corresponding Author:
Maksim A. Solovev, Goldberg Research Institute of Pharmacology and Regenerative Medicine, Tomsk National Research Medical Center of the Russian Academy of Science, 3 Lenina avenue, Tomsk 634009, Russia.
Email: ms1776882@gmail.com

of PTD is convulsions in the muscles of the diseased limb at night.[4-7]

Despite successes in the diagnosis, treatment, and prophylaxis of DVT, PTD is the most common complication of DVT and develops in 20% to 50% of patients even in anticoagulant therapy, determining a high incidence and mortality from PE and recurrent venous thrombosis.[4,5]

From the opinion of Kahn et al, PTD is a chronic and not fully studied complication of DVT. In this regard, the authors conducted multivariate regression analyses to evaluate the predictors of PTD and the efficacy of anticoagulant therapy in 145 patients from 13 Canadian and 1 US hospitals who received a 3-month course of warfarin treatment for 2 international normalized ratio (INR) targets: 2.5 and 1.7. After monitoring the patients for 2.2 years, the prevalence of PTD was 37%, and severe PTD was detected in 4% of patients, indicating that there was no effect of anticoagulant therapy on the risk of PTD. In addition, it has been established that mutations of factor (F) V Leiden and prothrombin are independent predictors of low risk and severity of PTD. However, according to researchers, this conclusion requires further evaluation in prospective studies.[6]

To identify risk factors for PTD and their effect on the course of PTD, Stain et al conducted a prospective follow-up of 406 patients after the first episode of DVT. Patients with recurrent DVT, deficiency of a natural inhibitor, lupus anticoagulant, with oncological diseases, and with long-term anticoagulants were excluded from the study. Results of the study showed that 43.3% of patients developed PTD, and among the risk factors for PTD, the most significant was proximal DVT.[7]

The effectiveness of preventing recurrent DVT and PE in the context of secondary thrombophilia (postthrombotic) is 5% to 15%. The authors during for 3 months examined the quality of prophylaxis with warfarin for recurrence of venous thromboembolic complications (DVT, PE, and complications of anticoagulant therapy) after a distal DVT in 40 patients. The results of the study showed that the therapeutic range of INR was detected only in 43% of those examined. At the same time, the recurrence rate of venous thrombosis was 5%, and hemorrhagic complications developed in 7.5% of cases. The authors conclude that in patients taking long-term indirect anticoagulants after distal DVT, the level of effective anticoagulation is reached in less than half of the observations and is the main cause of the high incidence of thrombotic and hemorrhagic complications.

New opportunities of pharmacological thromboprophylaxis of secondary thrombophilia were associated with the direct thrombin inhibitor—Dabigatran (Pradaxa, Boehringer Ingelheim, Germany).

Eriksson et al showed by conducting a randomized, double-blind trial of 2076 patients undergoing complete knee replacement who received dabigatran etexilate 150 mg and 220 mg once daily for 1to 4 hours after surgery. Patients were observed for 3 months. The primary outcome of the efficacy of the drug was assessed venographically or symptomatically, and the primary outcome of safety was the incidence of bleeding.

According to the researchers, dabigatran etexilate, an oral direct thrombin inhibitor, does not require monitoring or dose adjustment for prevention of venous thromboembolism (VTE) after knee replacement surgery.[8] The same authors in another study evaluated the efficacy and safety of dabigatran for extended thromboprophylaxis in 2055 patients undergoing total hip arthroplasty. Patients were randomized from 28 to 35 days of oral dabigatran at a dose of 220 mg once a day 1 to 4 hours after surgery. The primary outcome of drug efficacy was assessed by the incidence of proximal DVT or nonfatal PE, and the safety criterion for the drug was the frequency of cases of bleeding. According to the researchers, proximal DVT or nonfatal PE in the background of dabigatran prophylaxis occurred in 7.7% of cases, and clinically significant bleeding was detected in 1.4% of patients after total hip replacement.[8]

Friedman et al showed in 3 randomized, double-blind studies the safety of 220 mg and 150 mg dabigatran once daily with subcutaneous administration of 40 mg enoxaparin once daily or 30 mg twice daily in 8210 patients after planned hip and knee replacement. According to the authors, the cumulative result of major venous thromboembolism (proximal DVT and / or PE) and mortality associated with it were observed in 3.3% of the enoxaparin group and were recorded in 3.0% of cases after taking 220 mg of dabigatran and 3.8% examined on the background of taking 150 mg of the drug. Clinically significant bleeding was detected in 1.4% of patients on the background of taking 220 mg of dabigatran and in 1.1% of cases after taking 150 mg of the drug. Based on the results obtained, the authors conclude that in reducing the risk of severe VTE and associated with VTE mortality after arthroplasty of the hip joint or knee joint, dabigatran is not inferior in effectiveness to subcutaneous administration of enoxaparin and has a similar bleeding profile with it.[9]

In Denmark, regardless of dosage, dabigatran caused an increase in the risk of thromboembolic complications (TCs) in patients earlier treated with warfarin. So, Hernandez et al in a retrospective cohort study compared the risk of hemorrhage associated with dabigatran and warfarin in 9404 patients with newly diagnosed atrial fibrillation, of which 1302 patients took dabigatran and 8102 patients were treated with warfarin for 90 days. The authors identified 4 risk groups for bleeding: patients 75 years of age and older, African Americans, patients with chronic kidney disease, and persons with more than 7 concomitant diseases. The results of the study showed that when treating with dabigatran, a higher risk of clinical implementation of gastrointestinal and renal bleeding but a lower risk of intracranial hemorrhage was observed compared to warfarin. The maximum risk of clinically significant bleeding among users of dabigatran was identified for African Americans and patients with chronic kidney disease. The authors believe that dabigatran should be administered with caution to patients with a high risk of hemorrhagic complications of anticoagulant therapy.[10]

Despite the recommendations on the widespread use of dabigatran in patients with atrial fibrillation, according to Sorensen et al, real data on the practical use of the drug, its

efficacy, and safety are not fully understood. Based on this, the authors conducted a pharmacoepidemiological cohort study comparing the frequency of thrombotic and hemorrhagic complications in 52 366 patients with atrial fibrillation of which 1612 patients took dabigatran at a dose of 110 mg, and 1114 patients were treated with this drug at a dose of 150 mg. As a comparison, the study was performed in 49 640 patients who had anticoagulant therapy with warfarin. The analysis of thromboembolic events and bleeding took into account the adherence of patients to the recommendations of the European Agency for Medicine (EMA) for dabigatran. The results of the study showed that EMA recommendations for dabigatran were fulfilled by 90.3% of patients receiving 110 mg of dabigatran and 55.5% of patients treated with 150 mg of the drug. Among those who did not comply with the recommendations of the EMA were patients older than 80 years, patients with liver or kidney disease, and patients with a history of bleeding. Compared to warfarin, the hazard ratio of thrombotic complications for 110 mg of dabigatran was 3.52 and for 150 mg dabigatran was 5.79.[11]

In an observational study, Torben et al compared dabigatran with warfarin to prevent secondary strokes in 2398 patients with atrial fibrillation (AF) and a stroke or transient ischemic attack in history that started dabigatran at doses of 110 and 150 mg and continued anticoagulant therapy with this drug after course of treatment with warfarin. In patients who took warfarin and then switched to dabigatran at doses of 110 or 150 mg, a greater incidence of repeated strokes is recorded compared to patients who continued to take warfarin. Among patients who started dabigatran treatment, the incidence of stroke or transient ischemic attack for both doses of dabigatran was similar but less than warfarin. Based on these results, the authors believe that the administration of dabigatran following a course of treatment with warfarin increases the risk of stroke and transient ischemic attacks.[12]

Patients with AF, stroke, and transient ischemic attack in their history who took warfarin and then switched to the dabigatran experience recurrent stroke more frequently than patients who stuck to warfarin.[13] In comparison to warfarin, the use of dabigatran is associated with higher risk of massive bleeding and gastrointestinal bleeding but lower risk of intracranial hemorrhage.[10]

A serious obstacle to the "routine" use of dabigatran may be caused by thrombotic complications. The indirect anticoagulant warfarin inhibits the formation of factors VII and IX as well as inhibits thrombin generation and factor X shared by intrinsic and extrinsic coagulation pathways that significantly increase its anticoagulant effect, unlike dabigatran which inhibits only thrombin.[13,14-16]

Effectiveness and safety of dabigatran are associated with the monitoring and screening laboratory test for prevention of the risk of overdose. However, real clinical safety and efficacy of this drug in "routine" practice differ from the data of phase III clinical studies and cause ethical contradictions for practitioners. The absence of recognized laboratory markers evaluating the level of hypocoagulation and safe use of dabigatran

does not require control over blood coagulation system. In clinical practice, when contact activation is intense and local thrombin level is high, dabigatran concentrations in plasma may be insufficient to prevent thrombosis.[15] Dabigatran should be prescribed with caution, especially for patients at high risk.[16]

In the context of abovementioned difficulties, our research was carried out on the problems and contradictions of clinical use of the direct thrombin inhibitor dabigatran. The purpose is to study daily pharmacodynamics of dabigatran in healthy individuals and patients with PTD.

Materials and Methods

Study Design

We aimed to investigate the daily pharmacodynamics of dabigatran in healthy volunteers and patients with PTD.

Inclusion criteria. Availability of informed consent for the study; lack of participation in other studies; age older than 36 and younger than 45 years; disease duration of 1 to 2 years; absence of intolerance to drugs and allergic reactions; absence of prior treatment with disaggregates, anticoagulants, fibrinolytic drugs, and drugs that reduce inflammation of the vein wall; moderate pain; not requiring use of analgesics; slight / moderate edema; mild / moderate "venous lameness"; localized pigmentation; absence of ulcer; presence of symptoms of the disease; the patient is able to work without supporting means; and absence of concomitant diseases that can affect the process of thrombosis.

Exclusion criteria. Lack of informed consent for the study; patient's refusal to participate in this study; participation in other studies 6 months before the current study; age younger than 36 and older than 45 years; disease duration of more than 2 years; indication of intolerance to drugs and allergic reactions in the past; previous treatment with disaggregates, anticoagulants, fibrinolytic drugs, drugs that reduce inflammation of the veins 6 months before the present study; presence of contraindications to the use of dabigatran; kidney disease in anamnesis; body weight less than 50 kg; presence of strong pain, requiring pain medication; presence of expressed swelling, strong "venous lameness," common pigmentation, and ulcer; the patient can work for 8 hours only with the use of supportive means; presence of concomitant diseases that can affect the process of thrombosis: congenital or acquired diseases of the blood coagulation system, thrombocytopenia or functional defects of platelets, a recent biopsy or extensive trauma, and bacterial endocarditis.

Sampling Procedure

In a clinic of Goldberg Research Institute of Pharmacology and Regenerative Medicine, Tomsk National Research Medical Centre of the Russian Federation, a study was conducted. The sample consisted of 69 people (34 healthy volunteers and 35

patients with PTD: 20 men and 15 women) aged 36 ± 4.7 years. Patients and healthy volunteers signed an informed consent form to participate in the examination according to the WMA Declaration of Helsinki and approved by the Local Ethical Committee of Goldberg Research Institute of Pharmacology and Regenerative Medicine. The research was carried out on the own equipment of the Scientific Research Institute of Pharmacology. The examination included the analysis of complaints, case histories, and clinical checkup. A general examination was carried out in physical examination. Growth (m) and body mass (kg) were measured. Blood pressure (BP) level was studied in accordance with international recommendations by means of a 24-hour monitoring of BP using Meditech ABPM-04 (Meditech, Hungary). Blood chemistry test was done with the use of common laboratory techniques. The kidney and abdominal organs were examined using the ClearVue 550 ultrasound scanner (Philips, Boston, USA). Kidney disease in patients with PTD has not been identified.

The verification of PTD was carried out according to the data of ultrasound duplex scanning of deep veins of the lower extremities on ultrasound systems Logiq 400 (General Electric) and Sonos 5500 (Hewlett Packard, Palo Alto, USA). No violations of venous hemodynamics of the affected limbs were found in 4 men and 2 women. Infringements of a venous hemodynamics in the form of a reflux have been revealed in 16 men and 13 women (Table 1). The clinical characteristics of the examined patients are presented in Table 1.

Intervention

The hemostatic potential of whole blood was studied before taking dabigatran and 4, 8, 12, and 24 hours after a single dose of 150 mg. Thromboelastography (TEG) of the whole blood was used for integral assessment of all phases of blood coagulation and fibrinolysis.

Despite biased diagnostic value of the thromboelastographic method, we have chosen it as a basic method for integral assessment of all phases of blood coagulation and total lytic activity of the blood, characterizing spontaneous lysis of a clot. We opted for this method because it provides a comprehensive assessment of the hemocoagulation process in its dynamics with the analysis of the fibrin–platelet structure of the clot; it is easy to use, and there is a possibility of standardization of research and high efficiency in obtaining the results of rapid assessment of the state of coagulation hemostasis.[17-19] The study was performed on the thromboelastographer AGKM-01 (Ufa, Russian Federation). The recorder tape moves at 1 cm/min. In order to create conditions simulating blood clotting in the lumen of the vessel, the thromboelastogram was recorded at a constant temperature of 37°C, with a standard blood volume (0.36 mL) in silicone cuvettes and isolation of the sample from the influence of atmospheric air, which was achieved by applying a thin layer of indifferent oil to the blood surface after

Table 1. Clinical Characteristics of the Examined Patients With Post-thrombotic Disease According to the International Classification of CEAP.[a]

Indicators	Men, n = 20	Women, n = 15
Clinical symptoms		
Absence of symptoms of venous disease during examination and palpation	4	7
Telangiectasia / reticular veins	18	9
Varicose veins	20	15
Edema	16	13
Pigmentation and / or venous eczema	0	0
Lipodermatosclerosis	0	0
Skin changes and healed ulcer	0	0
Subjective symptoms (heaviness, feeling of bursting, convulsions, and so on)	18	14
Absence of subjective symptoms	2	1
Pain		
Absence	15	10
Moderate, not requiring the taking of analgesics	5	5
Strong, requiring pain medication	0	0
Etiology of the post-thrombotic disease		
Congenital disease	0	0
Primary with unknown cause	0	0
Secondary with a known cause: post-thrombotic, posttraumatic, and so on	20	15
Cannot determine the cause of the disease	0	0
Localization of the disease		
Popliteal	6	4
Veins of lower leg—anterior and posterior, tibial, peroneal (all paired)	14	11
No changes in the venous system	0	0
Outflow of damaged vein		
Reflux	16	13
Obstruction	0	0
Reflux + obstruction	0	0
No violations of venous outflow	4	2
"Venous lameness"		
Absence	10	8
Mild / moderate	10	7
Strong	0	0
Disability Rating Scale		
Asymptomatic course	15	10
The presence of symptoms of the disease, the patient is able to work and does without supporting means	5	5
The patient can work for 8 hours, only with the use of supportive means	0	0
The patient is incapacitated even with the use of supporting means	0	0
Comorbidities that could affect thrombosis: congenital or acquired diseases of the blood coagulation system, thrombocytopenia or functional defects of platelets, a recent biopsy or extensive trauma, and bacterial endocarditis	0	0

Abbreviations: CEAP, Comprehensive Classification System for Chronic Venous Disorders; n, number of observations.
[a]All indicators of the frequency of detected symptoms are presented in absolute values.

Table 2. Comparative Evaluation of the Functional State of the Coagulation and Anticoagulation Systems of Healthy Blood and Patients With Post-thrombotic Disease (X $\pm$ m).

Indicators	Healthy, n = 34	Patients with Post-thrombotic Disease, N = 35	
		PTD$_1$, n = 28	PTD$_2$, n = 7
Before taking 150 mg of dabigatran			
r, min	13.51 $\pm$ 0.24	7.24 $\pm$ 0.35[a], P = .03	8.24 $\pm$ 0.11[a], P = .05
k, min	7.48 $\pm$ 0.25	5.56 $\pm$ 0.22[a], P = .05	6.54 $\pm$ 0.31[a], P = .05
t, min	35.48 $\pm$ 1.81	29.33 $\pm$ 1.47[a], P = .05	40.11 $\pm$ 1.18[a], P = .05
MA, mm	45.59 $\pm$ 0.55	52.67 $\pm$ 3.07[a], P = .05	42.74 $\pm$ 2.27, P = .052
TLA, %	11.61 $\pm$ 1.67	9.96 $\pm$ 0.17[a], P = .04	15.10 $\pm$ 1.84[a], P = .05
ITP, rel. unit	6.25 $\pm$ 0.22	9.56 $\pm$ 0.29[a], P = .02	5.14 $\pm$ 2.13[a], P = .05

Abbreviations: PTD, post-thrombotic disease; r, reaction time, k, prothrombin time, t, fibrin–platelet clot formation; MA, maximum amplitude of TEG; TLA, total lytic activity of blood, ITP, thrombodynamic potential index, min, time in minutes.
[a]Significant differences from healthy indicators.

immersion of the recording cylinder. Blood samples were added to the cuvette preheated to 37°C directly from vein.[20]

The countdown began with the first drops of blood filling the cuvette. The following TEG parameters were calculated and analyzed: reaction time (r; minutes) characterizing phases I and II of blood coagulation; prothrombin time (k; min) reflecting phases II and III of blood coagulation; fibrin–platelet clot formation (t; min); maximum amplitude of TEG (MA; mm) describing the density of the clot, which (in turn) depends on retractile properties of platelets and the quantity of fibrinogen; total lytic activity of blood (TLA; %) characterizing spontaneous lysis of the clot over 1 hour; and index of thromodynamics potential (ITP, r.u.) reflecting the dynamic evolution of the clot.[21,22]

Statistical Analysis

Statistica 6.0 was used for statistical processing of the research results. All available data samples were tested in terms of normal distribution by the value of the coefficients of asymmetry and kurtosis. The hypothesis of the normality of distributions of random variables was accepted if the coefficients of asymmetry and kurtosis in absolute value did not exceed 3 times and 5 times, respectively, their standard deviations. For each sample, the mean value of the trait (X) and the mean error of the mean value (m) were calculated. The Wilcoxon test was used to assess the reliability of sample differences. Differences were considered valid at $P < .05$.

Research Results

Before taking 150 mg of dabigatran, there was a significant decrease in r and k in the patients. It indicates an increase in coagulation phases I, II and III. At the same time, the t, MA, TLA, and ITP in patients were characterized by multidirectional changes that served as a basis for their division into 2 subgroups: PTD$_1$ and PTD$_2$ (Table 2).

In subgroup PTD$_1$ (28 patients), t is shorter by 17.3% ($P = .05$), whereas in subgroup of PTD$_2$ (7 patients) this indicator increases by 13% ($P = .05$) compared to healthy individuals. A significant increase in ITP by 53% ($P = .02$) and MA by 15.5% ($P = .05$) from the indicators of healthy volunteers clearly reflect the increase in the structural properties of the clot in subgroup PTD$_1$. At the same time, the decrease in the values of ITP by 17.8% ($P = .05$) and the tendency to decrease in MA of TEG ($P > .05$) indicate a decrease in the structural properties of the clot in subgroup PTD$_2$ compared to healthy individuals.

The revealed features of changes in the coagulation link of hemostatic system of patients were accompanied by differences in the reaction of the blood anticoagulant system. In particular, TLA in subgroup PTD$_1$ decreased by 14.2% ($P = .04$) and in subgroup PTD$_2$ increased by 30.1% ($P = .05$), compared to healthy volunteers.

One of the possible mechanisms determining the revealed features in a coagulation link of hemostatic system of patients with PTD is associated with different thrombin activity in the analyzed subgroups, that is, higher thrombin activity in subgroup PTD1. It is possible that the structural hypocoagulation found in subgroup PTD2 is determined by high activity of the blood anticoagulation system, which determines the decrease in the clot density in comparison to subgroup PTD1 and healthy volunteers.

Thus, in comparison to healthy volunteers, chronometric and structural hypercoagulation is recorded in 80% of cases (PTD$_1$), whereas 20% of observations (PTD$_2$) makeup chronometric hypercoagulation caused by structural hypocoagulation. Prior to thromboprophylaxis of secondary thrombophilia with dabigatran to determine the risk of clinically significant bleeding, focus on the following indicators of thromboelastography: t, MA, ITP, and TLA. According to our data, markers of risk of hemorrhagic complications under dabigatran are TEG indicators lying within the reference values of the healthy volunteers: t, TLA, ITP, and MA. The results of pharmacodynamic evaluation of 150 mg of dabigatran in patients and healthy volunteers are presented on the Table 3.

Four hours after taking 150 mg of dabigatran (compared to healthy volunteers), r in subgroup PTD$_1$ shortens by 44.3% ($P = .001$), whereas in subgroup PTD$_2$ there is only a tendency to increase ($P > .05$), which, on the one hand, indicates an

Table 3. Comparative Evaluation of the Functional State of the Coagulating and Anti-Coagulating Blood Systems of Healthy and Patients with Post-Thrombotic Disease after taking 150 mg of Dabigatran (X ± m).

| Indicators | Healthy, n = 34 | Patients With Post-thrombotic Disease, N = 35 | |
		PTD$_1$, n = 28	PTD$_2$, n = 7
4 hours after taking 150 mg of dabigatran			
r, min	18.94 ± 0.78	10.17 ± 0.24^a, P = .001	20.40 ± 0.11, P = .058
k, min	9.66 ± 0.13	7.56 ± 0.22^a, P = .03	12.03 ± 0.22^a, P = .03
t, min	46.07 ± 1.55	43.40 ± 1.77, P = 0.052	49.94 ± 2.22^a, P = 0.03
MA, mm	39.70 ± 0.93	45.97 ± 3.12^a, P = .04	34.90 ± 1.88^a, P = .05
TLA, %	12.97 ± 2.55	11.96 ± 0.17, P = .052	15.10 ± 1.84^a, P = .04
ITP, rel. unit	7.66 ± 0.18	6.56 ± 0.29^a, P = .053	3.22 ± 1.18^a, P = .02
8 hours after taking 150 mg of dabigatran			
r, min	14.49 ± 0.93	9.09 ± 0.59^a, P = .03	12.35 ± 0.20^a, P = .05
k, min	8.55 ± 0.10	6.03 ± 0.38^a, P = .03	9.97 ± 0.43^a, P = .04
t, min	39.15 ± 1.86	35.78 ± 1.77, P = .052	45.13 ± 1.76^a, P = .04
MA, mm	42.83 ± 0.82	50.01 ± 2.11^a, P = .04	35.99 ± 1.72^a, P = .05
TLA, %	12.00 ± 2.34	9.33 ± 0.20^a, P = .04	14.85 ± 1.52^a, P = .04
ITP, rel. unit	7.13 ± 0.10	9.09 ± 0.19^a, P = .03	3.93 ± 1.21^a, P = .02
12 hours after taking 150 mg of dabigatran			
r, min	13.51 ± 0.24	7.24 ± 0.35^a, P = .03	10.24 ± 0.11^a, P = .04
k, min	7.48 ± 0.25	5.56 ± 0.12^a, P = .04	6.63 ± 0.32^a, P = .05
t, min	39.99 ± 0.87	28.66 ± 1.43^a, P = .04	40.77 ± 1.07, P = .052
MA, mm	45.30 ± 0.64	51.54 ± 2.02^a, P = .04	41.01 ± 1.13, P = .051
TLA, %	11.33 ± 1.42	8.34 ± 0.23^a, P = .04	14.90 ± 0.96^a, P = .04
ITP, rel. unit	6.13 ± 0.25	9.24 ± 0.21^a, P = .03	4.09 ± 1.42^a, P = .04
24 hours after taking 150 mg of dabigatran			
r, min	13.48 ± 0.20	7.22 ± 0.30^a, P = .02	10.26 ± 0.10^a, P = .03
k, min	7.44 ± 0.28	5.60 ± 0.28^a, P = 0.03	6.57 ± 0.55^a, P = 0.05
t, min	35.22 ± 1.97	28.77 ± 1.44^a, P = .02	40.66 ± 1.10^a, P = .04
MA, mm	45.90 ± 0.88	52.70 ± 2.93^a, P = .04	42.30 ± 0.04, P = .051
TLA, %	11.65 ± 1.63	9.88 ± 0.15^a, P = .05	15.04 ± 1.95^a, P = .04
ITP, rel. unit	6.20 ± 0.11	9.56 ± 0.29^a, P = .03	5.00 ± 1.13^a, P = .04

Abbreviations: PTD, post-thrombotic disease; r, reaction time, k, prothrombin time, t, fibrin–platelet clot formation; MA, maximum amplitude of TEG; TLA, total lytic activity of blood, ITP, thrombodynamic potential index; min, time in minutes.
^{a}Significant differences from healthy indicators.

acceleration of hemocoagulation phases I and II caused by dabigatran in subgroup PTD$_1$ and on the other hand demonstrates similar effect of the drug on these phases of coagulation in healthy volunteers and patients in subgroup PTD$_2$. In this case, k decreased by 21.7% (P = .03) in subgroup PTD$_1$ and increased in subgroup PTD$_2$ by 24.5% (P = .03), which shows the acceleration of coagulation phase III after the intake of 150 mg of the drug in subgroup PTD$_1$ and slowing down of this phase in PTD$_2$.

A similar dynamics was revealed in the t. In particular, in subgroup PTD$_1$, there was a tendency to increase the fibrin–platelet structure of the clot, whereas in subgroup PTD$_2$ there was a statistically significant increase in t by 24.6% (P = .03), compared to the values of healthy volunteers.

The density of the blood clot, as measured by the indicator MA after 4 hours after intake of 150 mg of dabigatran, increased by 15.8% (P = .04) in subgroup PTD$_1$ and decreased by 12.1% % (P = .05) in subgroup PTD$_2$ in comparison to the indicators of healthy individuals. However, the thrombodynamic potential index (ITP) decreased in both the groups: by

14.3% (P = .05) and 60% (P = .02) in subgroup PTD$_1$ and subgroup PTD$_2$, respectively.

The reactions of the blood anticoagulant system in the analyzed subgroups of patients were similar. In particular, TLA in subgroup PTD$_2$ increased by 16.4% (P = .04), while in subgroup of PTD$_1$ only the tendency to its increase was registered (Table 3).

Our pharmacodynamic study of dabigatran 4 hours after the intake clearly show that 150 mg of the drug is not sufficient in 80% of cases (subgroup PTD$_1$) and redundant in 20% of observations (subgroup PTD$_2$) for secondary thromboprophylaxis of thrombophilia. According to our data, 4 hours after the intake of 150 mg of the drug, the following parameters of TEG can serve as markers for the risk of hemorrhagic complications in thromboprophylaxis of dabigatran: increase in r, k, t, and MA within the reference values of the healthy established before taking the drug.

Eight hours after the intake of 150 mg of dabigatran (compared to healthy volunteers), decrease in reaction time was recorded in both subgroups of patients (r): in subgroup PTD$_1$ by 37.3% (P = 0.03) and in subgroup PTD$_2$ by 14.8% (P =

.05), indicating the acceleration of phases I and II. In this case, k decreased by 29.5% ($P = .03$) in subgroup PTD_1 and increased by 16.6% ($P = .04$) in subgroups PTD_2, which shows the acceleration of phase III of blood coagulation in subgroup PTD_1 and a further slowdown of this phase in subgroup PTD_2. However, t in subgroup PTD_1 decreased slightly, while in subgroup PTD_2, there was a significant increase in t by 15.3% ($P = .04$), compared to the values of healthy individuals (Table 3).

The MA demonstrates that density of the clot increased 8 hours after the intake of 150 mg of dabigatran by 16.8% ($P = .04$) in the PTD_1 and decreased by 16% ($P = .05$) in PTD_2, in comparison to indicators of healthy individuals. The ITP increased in PTD_1 by 27.5% ($P = 0.03$) and decreased by 44.9% ($P = 0.02$) in PTD_2 compared to healthy volunteers. These changes show a different density of the clot in the analyzed subgroups of patients.

The reaction of blood anticoagulant system in the analyzed subgroups of patients was also opposite. In particular, TLA in PTD_1 decreased by 223% ($P = .04$) and in PTD_2 increased by 23.8% ($P = .04$), which reflects structural hypercoagulation in PTD_1 and structural anticoagulation in PTD_2, caused by chronometric hypercoagulation in both subgroups (Table 3).

Thus, in order to prevent hemorrhagic complications in patients with PTD, 8 hours after the intake of 150 mg of Dabigatran, the following indicators of TEG should be monitored: k, MA, ITP, and TLA.

The dynamics of TEG indicators 12 hours after the drug administration showed that when continuing chronometric hypercoagulation in both subgroups, PTD_1 revealed a significant reduction in the t, a decrease in TLA, and an increase in the density of the blood clot (ITP). Along with this, a completely opposite deviation of these indicators was revealed in PTD_2: a statistically significant increase in blood anticoagulation activity (TLA) and decrease in the density of the clot (ITP) caused by the tendency to increase t (Table 3).

Thus, in order to prevent hemorrhagic complications in patients with PTD 12 hours after receiving a single 150 mg dose of dabigatran, the degree (depth) of blood anticoagulation must be monitored by the following indicators of TEG: t, MA, ITP, and TLA.

Twenty-four hours after receiving 150 mg of dabigatran (compared to healthy volunteers), r shortens in both subgroups of patients: in PTD_1 by 46.4% ($P = 0.02$) and in PTD_2 by 23.9% ($P = .03$), indicating the acceleration of phases I and II of blood coagulation. As a result, k reduced by 24.7% ($P = .03$) in PTD_1 and by 11.7% ($P = .05$) in PTD_2. This shows the acceleration of phase III of blood coagulation is more pronounced in subgroup PTD_1. However, t in the subgroups was completely opposite. Along with a significant decrease in the absolute value of this indicator in subgroup PTD_1, a significant increase in the indicator t by 15.5% ($P = .04$) was recorded in subgroup PTD_2 in comparison to healthy volunteers (Table 3).

According to the indicator MA, the density of the clot 24 hours after the intake of 150 mg of dabigatran changed oppositely: increased by 14.8% ($P = 0.04$) in PTD_1 and a

decreased in PTD_2, compared to healthy individuals. The ITP increased in PTD_1 by 54.2% ($P = .03$). But in PTD_2, the ITP decreased by 19.4% ($P = .05$) compared to healthy volunteers, which indicates the different density of the blood clot in the analyzed subgroups of patients.

The reactions of blood anticoagulant system in the analyzed subgroups of patients were also opposite. In particular, in PTD_1, TLA decreased by 15.2% ($P = .05$) and in PTD_2, on the contrary, increased by 29.1% ($P = .04$), which demonstrates structural hypercoagulation in PTD_1 and structural anticoagulation in PTD2 caused by chronometric hypercoagulation in both subgroups (Table 3).

Thus, a day after receiving 150 mg of dabigatran, it is necessary to control the degree of anticoagulation by the TEG indicators such as t, MA, ITP, and TLA to prevent bleeding in patients with PTD.

Discussion

The absence of recognized laboratory markers evaluating the level of anticoagulation under dabigatran and safe use of dabigatran that does not require control over blood coagulation system replicated by many, including Russian hemostasiologists,[10-13,14-16,23-25] are the main causes of ethical contradictions for practitioners.[23]

Most of the work on assessing hemorrhagic and thrombotic complications in the treatment of patients with various diseases with dabigatran is not preventive in that it records the incidence of clinically significant complications or identifies risk factors that are not related to the patient's blood coagulation system. The innovation of our study is a method for assessing the potential risk of implementation these complications on dabigatran, based on daily monitoring of coagulation, anticoagulant, and fibrinolytic systems of the patient.

Our research into the "routine" use of a direct thrombin inhibitor dabigatran in secondary thrombophilia (case of patients with PTD) clearly demonstrates the need for hemostatic control over the level of anticoagulation in every patient receiving Dabigatran. At the same time, the effective dose of the drug should be prescribed by a clinician taking into account the safety of the drug, which, according to our data, is determined by the indicators of TEG within the daily pharmacodynamics of dabigatran.

Before starting thromboprophylaxis of secondary thrombophilia or treatment for DVT, markers of safe use of dabigatran must be kept in mind, that is, TEG indicators within the reference values of the healthy before taking the drug such as t, TLA, ITP, and MA.

According to our data, 4 hours after receiving 150 mg of the drug, the following TEG indicators can serve as markers of risk for hemorrhagic complications in dabigatran thromboprophylaxis: increase in r, k, t, and MA within the reference values of the healthy established before taking the drug.

Indicators k, MA, ITP, and TLA must be monitored 8 hours after the administration of 150 mg of dabigatran to prevent hemorrhagic complications in patients with PTD. In order to

prevent hemorrhagic complications in patients with PTD 12 hours after receiving a single dose of dabigatran, the degree (depth) of anticoagulation must be monitored by the following TEG indicators: t, MA, ITP, and TLA.

A day after receiving 150 mg of dabigatran, the degree of anticoagulation must be controlled to prevent bleeding in patients with PTD: t, MA, ITP, and TLA.

In conclusion, it should be noted that the most complete information about safety and efficacy of dabigatran in a particular patient with a specific disease can be obtained in prospective long-term studies. A clear example is the 30-year history of working out optimal schemes of anticoagulant therapy with unfractionated heparin and a vitamin K antagonist, which defined "therapeutic" anticoagulation range that provides maximum reduction in risk of developing both venous and arterial thrombosis while minimizing the risk of bleeding.[23-24]

Conclusion

Daily monitoring of the depth of anticoagulation on dabigatran in patients with PTD is consistent with the principle of personalized medicine and significantly simplifies the procedure for the safe use of the drug in real clinical practice in each patient. The following indicators of TEG within the reference values of healthy before taking the drug, t, TLA, ITP and MA, are markers for the safe use of dabigatran prior to the initiation of thromboprophylaxis of secondary thrombophilia or treatment of DVT.

After 4 hours of taking 150 mg of the drug with markers of risk of hemorrhagic complications with dabigatran thromboprophylaxis, the following TEG indices can be used: increase in r, k, t, and MA within the reference values of healthy ones established prior to taking the drug.

Eight hours after taking dabigatran 150 mg to prevent hemorrhagic complications in patients with PTD, the following indicators of TEG should be monitored: k, MA, ITP, and TLA.

Twelve hours after taking a single dose of dabigatran 150 mg, the degree (depth) of hypocoagulation in patients with PTD should be monitored by the following indicators of TEG: t, MA, ITP, and TLA.

One day after taking 150 mg of dabigatran with the goal of preventing clinically significant bleeding in patients with PTD, the depth of anticoagulation should be monitored by the following indices of TEG: t, MA, ITP, and TLA.

Thus, treatment with dabigatran in patients with PTD with chronic chronometric hypercoagulation and structural hypocoagulation before the administration of the drug is fraught with excessive anticoagulation and a high risk of clinically significant bleeding. In patients with PTD with detected chronometric and structural hypercoagulability before taking a direct thrombin inhibitor, treatment with dabigatran is fraught with possible inadequate anticoagulation and a high risk of clinically significant relapses of thromboses.

References

1. Spencer FA, Emery C, Lessard D, et al. The Worcester Venous Thromboembolism study: a population-based study of the clinical epidemiology of venous thromboembolism. *J Gen Intern Med*. 2006;21(7):722-727.
2. Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. *Lancet*. 2012;379(9828):1835-1846.
3. Christiansen SC, Cannegieter SC, Koster T, Vandenbroucke JP, Rosendaal FR. Thrombophilia, clinical factors, and recurrent venous thrombotic events. *JAMA*. 2005;293(19):2352-2361.
4. Kahn SR, Shrier I, Julian JA, et al. Determinants and time course of the postthrombotic syndrome after acute deep venous thrombosis. *Ann Intern Med*. 2008;149(10):698-707.
5. Kahn SR. How I treat postthrombotic syndrome. *Blood*. 2009; 114(21):4624-4631.
6. Kahn SR, Kearon C, Julian JA, et al. Predictors of the postthrombotic syndrome during long-term treatment of proximal deep vein thrombosis. *J Thromb Haemost*. 2005;3(4):718-723.
7. Stain M, Schönauer V, Minar E, et al. The post-thrombotic syndrome: risk factors and impact on the course of thrombotic disease. *J Thromb Haemostas*. 2005;3(12):2671-2676.
8. Eriksson BI, Dahl OE, Rosencher N, et al. RE-MODEL Study Group Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. *J. Thromb. Haemost*. 2007;5:2178-2185.
9. Friedman RJ, Dahl O, Rosencher N, et al. Dabigatran versus enoxaparin for prevention of venous thromboembolism after hip or knee arthroplasty: a pooled analysis of three trials. *Thromb Res*. 2010;126(3):175-182.
10. Hernandez I, Baik SH, Piñera A, Zhang Y. Risk of bleeding with dabigatran in atrial fibrillation. *JAMA Intern Med*. 2015;175(1): 18-24.
11. Sørensen R, Gislason G, Torp-Pedersen C, et al. Dabigatran use in Danish atrial fibrillation patients in 2011: a nationwide study. *BMJ Open*. 2013;3(5): e002758.
12. Larsen TB, Rasmussen LH, Gorst-Rasmussen A, Skjøth F, Lane DA, Lip GY. Dabigatran and warfarin for secondary prevention of stroke in atrial fibrillation patients: a nationwide cohort study. *Am J Med*. 2014;127(12):1172-1178.
13. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *New Engl J Med*. 2009; 361(12):1139-1151.
14. Eikelboom JW, Connolly SJ, Brueckmann M, et al. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med*. 2013;369(13):1206-1214.

15. Eikelboom JW, Connolly SJ, Brueckmann M, et al. Efficacy and safety of dabigatran etexilate and warfarin in "real-world" patients with atrial fibrillation: a prospective nationwide cohort study. *J Am Coll Cardiol*. 2013;61(22):2264-2273.

16. Serdechnaya EV, Yurieva SV, Ripple IN. Prevention of stroke in patients with atrial fibrillation in the practice of a physician. *Difficult Patient*. 2016;14:7-10.

17. Baluda VP, Barkagan ZS, Goldberg ED. *Laboratory methods of hemostasis*. Tomsk: Publishing house of Tomsk University; 1980: 309.

18. Tyutrin II, Udut VV, Zhuravlev VI, et al. Informative method of thromboelastography in the evaluation of coagulation hemostasis in cancer patients. *Laboratory*. 1985;10:600-604.

19. Yamakage M, Tsujiguchi N, Kohro S, Tsuchida H, Namiki A. The usefulness of celiteactivated thromboelastography for evaluation of fibrinolysis. *Can J Anaesth*. 1998;45(10):993-996.

20. Udut VV, Tyutrin II, Solov'ev MA, et al. Global tests in evaluation of the function of proand anticoagulant systems: present and future. *Bull Experiment Biol Med*. 2015;159(2):205-208.

21. Tyutrin II, Udut VV, Shpisman MN. Patent N 1110444 of the USSR. A method of evaluating thromboplastin. *Bull Invent*. 1984;32:34-38.

22. Udut VV. *Evaluation of Thrombosis in Patients with Gastric and Lung Cancer Stage III and IV Abstract of the Candidate's Thesis*. Tomsk: Tomsk Scientific Center of the Siberian Branch of the Russian Academy of Medical Sciences, 1985: 20.

23. Kotelnikov MV. Anticoagulant therapy in the prevention and treatment of thrombosis: international recommendations and real clinical practice. *Gen Med*. 2012;4:20-37.

24. Kotelnikov MV. Choice of antithrombotic drugs in real clinical practice, Proceedings of the XX Anniversary of The russian national congress "human and medicine". *Lectures Practitioners*. 2014;1:114-147.

25. Stangier J, Rathgen K, Stähle H, Gansser D, Roth W. The pharmacokinetics, pharmacodynamics and tolerability of dabigatran etexilate, a new oral direct thrombin inhibitor, in healthy male subjects. *Br J Clin Pharmacol*. 2007;64(3): 292-303.