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ORIGINAL ARTICLE

Effect of *CYP3A4*, *CYP3A5*, *ABCB1* Gene Polymorphisms on Rivaroxaban Pharmacokinetics in Patients Undergoing Total Hip and Knee Replacement Surgery

Dmitry Sychev[1] · Radik Minnigulov[2] · Pavel Bochkov[3] · Kristina Ryzhikova[4] · Irina Yudina[2] · Aleksey Lychagin[5] · Tatyana Morozova[6]

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Abstract

Introduction Population ageing in developed countries will inevitably increase the need for knee and hip replacement surgery. Over the years, direct oral anticoagulants, such as rivaroxaban, have been widely used for thromboprophylaxis in patients undergoing knee and hip replacement surgery. The study of pharmacogenetic characteristics of rivaroxaban is important for enhancing the effectiveness and safety of rivaroxaban thromboprophylaxis.

Aim Evaluation of *CYP3A4*, *CYP3A5* and *ABCB1* gene polymorphisms influence on rivaroxaban pharmacokinetics and prothrombin time dynamics in patients undergoing total hip and knee replacement surgery.

Methods The study included 78 patients undergoing total hip and knee replacement surgery. The patients received 10 mg of rivaroxaban once a day. Genotyping of polymorphisms *ABCB1* rs1045642, *ABCB1* rs4148738, *CYP3A4* rs35599367 and *CYP3A5* rs776746 was performed. Peak steady-state and trough steady-state rivaroxaban concentrations were determined. Prothrombin time was also evaluated.

Results The study revealed the following haplotypes: (1) *ABCB1* rs1045642—*CYP3A4* rs35599367 and (2) *ABCB1* rs4148738—*CYP3A4* rs35599367. The analysis of the peak steady-state rivaroxaban concentration between mutant haplotypes and wild haplotypes revealed no significant differences. However, there was a statistically significant average correlation between peak steady-state rivaroxaban concentration and prothrombin time ($r = 0.421$; $r^2 = 0.178$; $p < 0.001$).

Conclusion No significant difference was identified in peak steady-state rivaroxaban concentration between mutant haplotypes and wild haplotypes. The revealed statistically significant average correlation between the prothrombin time and peak steady-state rivaroxaban concentration is important in clinical practice for assessing the anticoagulant activity of rivaroxaban.

Keywords Rivaroxaban · Pharmacogenetics · Gene polymorphisms · Drug concentration · P-glycoprotein · Thromboprophylaxis

1 Introduction

According to the Global Orthopaedic Registry, the average age of patients undergoing hip and knee replacement surgery is about 70 years old [1]. In the developed countries the need for such arthroplasties is growing together with population aging. For example, the 2005–2030 US forecast has the increasing need for primary total hip replacement surgery (THR) of 174%, that for primary total knee replacement surgery (TKR)—of 673% [2].

THR and TKR patients are susceptible to a high risk of venous thrombosis: without anticoagulant thromboprophylaxis, the risk of deep vein thrombosis (DVT) in such patients rises to circa 60% [3]. Approximately 1 in every 500 patients that undergo THR can develop a fatal case of pulmonary embolism (PE) [4].

The recent addition to the row of thromboprophylaxis drugs commonly prescribed after THR and TKR are direct oral anticoagulants, which are easier to use and safer than warfarin. For example, rivaroxaban, a direct factor Xa inhibitor. In 2011, rivaroxaban was approved by FDA as a preventive medication for DVT and PE after THR and TKR [5].

✉ Radik Minnigulov
radik.minnigulov@gmail.com
https://internist.ru/lectors/detail/minnigulov-radik-miskhatovich/

Extended author information available on the last page of the article

Approximately 2/3 of a rivaroxaban dose undergo metabolic transformation. Rivaroxaban is metabolized by *CYP3A4*/5 by about 18%, while CYP2J2 ensures metabolization of approximately 14%. CYP-independent amide bonds hydrolysis contributes other 14% [6]. About 36% of the drug is eliminated unchanged with urine: 30% through active renal secretion, 6%—via glomerular filtration [7]. The transporters involved in the active renal secretion of rivaroxaban are P-glycoprotein and Breast Cancer Resistance Protein (BCRP) [8]. Gastrointestinal tract clears 28% of rivaroxaban dose: 7% unchanged, 9% as metabolite M-1 and 12% as further minor metabolites [6].

Co-administration of rivaroxaban with drugs that share its metabolic and excretory pathways can affect rivaroxaban exposure. For example, ketoconazole and ritonavir are strong CYP3A4 and P-glycoprotein inhibitors. Co-administration of rivaroxaban 10 mg once daily and ketoconazole 400 mg once daily led to a 2.58-fold increase in the AUC of rivaroxaban and a 1.72-fold increase in the C_{max} of rivaroxaban. Ritonavir also affected rivaroxaban exposure; the AUC and C_{max} of rivaroxaban increased by 2.53- and 1.55-fold, respectively [8].

Polymorphisms of genes encoding the above-listed isoenzymes and transporters can impair their function and modify the pharmacokinetics of rivaroxaban, which can adversely affect both safety and efficacy of the drug.

Thus, the study aims to evaluate the influence of *CYP3A4*, *CYP3A5* and *ABCB1* polymorphisms on the prothrombin time dynamics and rivaroxaban pharmacokinetics among patients undergoing total hip and knee replacement surgery.

2 Methods

The study was conducted from June to August 2017 at (1) Clinic of Traumatology, Orthopaedics and Joint Pathology (Sechenov University), (2) Department of Clinical Pharmacology and Propedeutics of Internal Diseases (Sechenov University) and (3) the R&D Center of Russian Medical Academy of Continuous Professional Education. Seventy-eight THR and TKR patients were enrolled; Table 1 contains detailed information about their condition. The study protocol was reviewed and approved by the local ethics committee of Sechenov University (meeting minutes № 03-17 of 2017.04.19). All the patients in the study signed a voluntary informed consent; their data were recorded in the impersonal patient cards. In accordance with the drug administration instructions, TKR patients were receiving 10 mg of rivaroxaban once daily for 14 days after the replacement, THR patients—same dose, once daily, for 35 days after the replacement surgery.

Table 1 Patients clinical characteristics

Number of patients	78
Sex (male/female)	22/56
Age (years)	59 ± 11[a]
Total hip replacement / total knee replacement surgery	26/52
Rivaroxaban $C_{max,ss}$ (ng/ml)	144.3 ± 72.8[a]
Body weight (kg)	84.4 ± 13.1[a]

[a]Data are presented as mean ± standard deviation

2.1 Assessment of Rivaroxaban Plasma Concentrations

To determine a trough steady-state plasma concentration of rivaroxaban ($C_{min,ss}$ of rivaroxaban), venous blood was sampled on the 3rd day of the course, 1 hour before the next administration. To determine the peak steady-state plasma concentration of rivaroxaban ($C_{max,ss}$ of rivaroxaban), the samples were taken 3 hours after administration. 6 ml Vacuette® vacuum tubes with lithium heparin were used for the purposes of blood collection.

The concentration of rivaroxaban in the blood was determined by high performance liquid chromatography (HPLC) with mass spectrometry detection. The Agilent 1200 Series HPLC System, which includes a quad pump, a mobile phase degasser and a column thermostat was used to analyze the samples; the column was Agilent Extend-C18 (length—100 mm; internal diameter—2.1 mm; particle size—3.5 µm). During separation, the temperature of the column was 40 °C. Mobile phase: solution A (50 ml of 0.1 M ammonium acetate solution and 5 ml of formic acid diluted with water deionized to the total volume of 1 l) and solution B (50 ml of 0.1 M ammonium acetate solution and 5 ml of formic acid diluted with acetonitrile to the total volume of 1 l). Chromatographic separation was performed in the isocratic elution mode with the A:B ratio 70:30. The mobile phase flow rate was 0.3 ml/min, introduced sample volume—10 µl. The analysis lasted for 7 min.

The research was done on the Agilent Triple Quad LC/MS 6410 mass spectrometer (triple quadrupole type); the mode of electrospray ionization—was positive; rivaroxaban spectra were registered in the many-molecule reaction mode, the gas was sprayed at 35 psi, the drying gas volume rate 11 l/min, temperature 350 °C, the fragmentation voltage value 135 V, collision cell voltage—25 V. Sample preparation technique—precipitation of plasma proteins. Plasma samples were thawed at room temperature. Then, 100 µl of plasma was transferred to Eppendorf tubes, introducing 250 µl of 0.1% HCl and methanol (9:1) solution thereto, using the Vortex shaker to mix the liquid,

letting it sit for 10 min and then mixing it again. Further on, the obtained samples were centrifuged for 10 min at 10,000 rpm. The supernatant layer was transferred to chromatographic vials and placed on the autosampler.

To determine rivaroxaban $C_{min,ss}$ blood samples from 75 out of 78 patients were taken, to determine rivaroxaban $C_{max,ss}$—from 70 patients. The lower limit of rivaroxaban detection was ≤ 25 ng/ml; rivaroxaban $C_{max,ss}$ > 25 ng/ml in 66 patients, rivaroxaban $C_{min,ss}$ > 25 ng/ml in 21 patients was registered.

2.2 Prothrombin Time Registration

For assessment of prothrombin time (PT) venous blood was collected when samples to determine rivaroxaban concentration were taken: 1 h before the patients took rivaroxaban (PT1) and 3 hours after (PT2); the samples were put into 2.7 ml BD Vacutainer® vacuum tubes with 3.2% sodium citrate. PT was determined with the help of Techplastin-test (Tekhnologiya-Standard; Russia) in accordance with the manufacturer's instructions.

2.3 Genotyping

Venous blood was drained into 4 ml Vacuette® vacuum tubes with EDTA-K3 anticoagulant. Genomic DNA was extracted from whole blood using kits of company "Syntol" (Moscow, Russian Federation). Single-nucleotide polymorphisms (SNPs) *ABCB1* rs1045642 and *CYP3A5* rs776746 were determined by real-time polymerase chain reaction (Real-Time PCR) using "SNP-Screen" kits of "Syntol" (Moscow, Russian Federation). The program included preliminary denaturation at 95 °C for 3 min, 40 cycles (15 s each) denaturation at 95 °C, annealing at 60 °C for 40 s. SNPs *ABCB1* rs4148738 and *CYP3A4* rs35599367 were detected by real-time polymerase chain reaction (Real-Time PCR) with "TaqMan® SNP Genotyping Assays" of Applied Biosystems® (Foster City, California, USA) and "Q5® HF DNA Polymerase" of New England Biolabs (Ipswich, Massachusetts, USA). The program included preliminary denaturation at 95 °C for 2 min, 39 cycles (15 s each) denaturation at 95 °C, annealing at 56 °C for 1 min. Polymorphisms were detected using CFX96 Touch Real-Time PCR Detection System (Bio-Rad Laboratories, Inc., USA) at the R&D Center of Russian Medical Academy of Continuous Professional Education.

2.4 Statistical Analyses

The studied polymorphism genotypes frequency distribution was tested for compliance with the Hardy–Weinberg equilibrium using an online calculator [9]. Mann–Whitney criteria were applied to determine statistical significance of differences between the results. Pearson correlation coefficient enabled the correlation analysis. The probability values below 0.05 were considered statistically significant. IBM SPSS PASW Statistics 18 (release of 2009) software was used to process the results.

3 Results

SNPs *ABCB1* rs1045642 and *ABCB1* rs4148738 demonstrated no difference from the Hardy–Weinberg equilibrium. The compliance of genotype distribution of SNPs *CYP3A4* rs35599367 and *CYP3A5* rs776746 to the Hardy-Weinberg equilibrium was impossible to assess as there were no carriers of homozygous genotype of SNP *CYP3A4* rs35599367 in the studied group, and no carriers of wild-type genotype of SNP *CYP3A5* rs35599367 (Table 2).

Table 3 features mean values of rivaroxaban $C_{max,ss}$ and SNPs *ABCB1* rs1045642, *ABCB1* rs4148738, *CYP3A4* rs35599367 and *CYP3A5* rs776746.

The influence of each SNP on rivaroxaban $C_{max,ss}$ was assessed. No increase in rivaroxaban $C_{max,ss}$ among heterozygous SNPs *ABCB1* rs1045642, *ABCB1* rs4148738 was found in comparison with wild-type genotype of these SNPs ($p = 0.306$ and $p = 0.391$, respectively; Figs. 1, 2). Homozygous SNPs *ABCB1* rs1045642, *ABCB1* rs4148738 also did not show any increase in rivaroxaban $C_{max,ss}$ in

Table 2 Genotype distribution of SNPs *ABCB1* rs1045642, *ABCB1* rs4148738, *CYP3A4* rs35599367 and *CYP3A5* rs776746 in patients undergoing total knee or total hip replacement surgery (n = 78)

Genotypes	Number of patients	Frequency	Hardy–Weinberg equilibrium (HWE)	
			χ^2	p value
ABCB1 rs1045642				
C;C	19	0.244	1.68	0.194
C;T	33	0.423		
T;T	26	0.333		
ABCB1 rs4148738				
C;C	23	0.295	0.175	0.676
C;T	37	0.474		
T;T	18	0.231		
CYP3A4 rs35599367				
C;C	73	0.936	— [a]	— [a]
C;T	5	0.64		
CYP3A5 rs776746				
A;G	10	0.128	— [a]	— [a]
G;G	68	0.872		

[a]The compliance of SNPs *CYP3A4* rs35599367 and *CYP3A5* rs776746 to the Hardy–Weinberg equilibrium was impossible to assess

Table 3 The mean values of rivaroxaban $C_{max,ss}$ and SNPs *ABCB1* rs1045642, *ABCB1* rs4148738, *CYP3A4* rs35599367 and *CYP3A5* rs776746 in patients undergoing total knee or total hip replacement surgery (n = 78)

	ABCB1 rs1045642			*ABCB1* rs4148738			*CYP3A4* rs35599367		*CYP3A5* rs776746	
	C;C (n = 16)	C;T (n = 29)	T;T (n = 19)	C;C (n = 19)	C;T (n = 29)	T;T (n = 16)	C;C (n = 59)	C;T (n = 5)	A;G (n = 7)	G;G (n = 57)
Rivaroxaban $C_{max,ss}$, ng/ml Mean ± SD	156.62± ±79.76	132.1± ±64.17	152.56± ±80.1	153.2± ±80.7	130.7± ±59.8	158.3± ±84.3	143.8± ±73.8	150.5± ±67.9	187.0± ±100.5	139.1± ±68.0

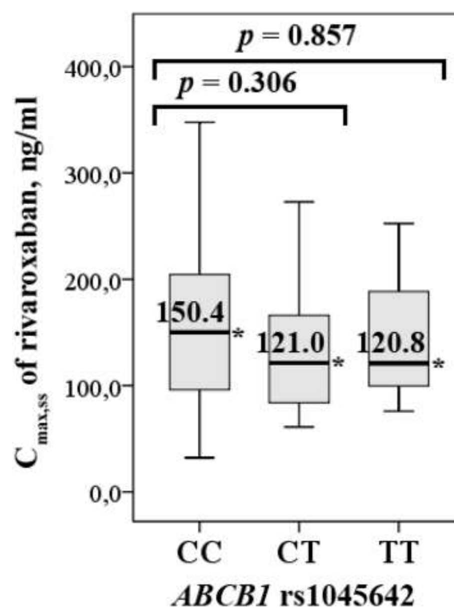

Fig. 1 Distribution of $C_{max,\ ss}$ of rivaroxaban depending on the genotype for SNP *ABCB1* rs1045642. *Median $C_{max,ss}$ of rivaroxaban

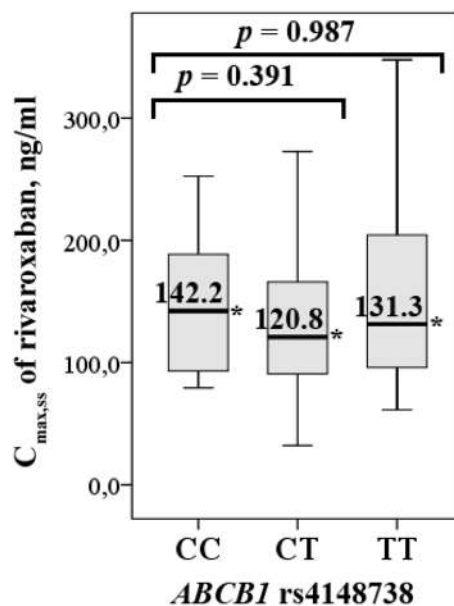

Fig. 2 Distribution of $C_{max,\ ss}$ of rivaroxaban depending on the genotype for SNP *ABCB1* rs4148738. *Median $C_{max,ss}$ of rivaroxaban

comparison with wild genotype of these SNPs ($p = 0.857$ and $p = 0.987$, respectively; Figs. 1, 2). A statistically significant difference between rivaroxaban $C_{max,ss}$ for *CYP3A4* rs35599367 (C;C) and *CYP3A4* rs35599367 (C;T) was not observed ($p = 0.716$; Fig. 3). Besides, a statistically significant difference between rivaroxaban $C_{max,ss}$ was not

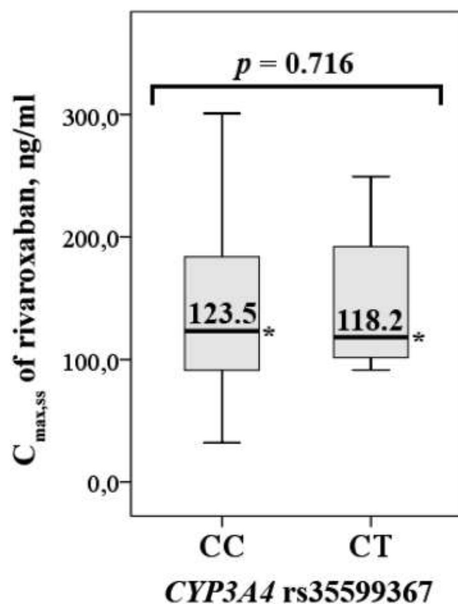

Fig. 3 Distribution of $C_{max,\ ss}$ of rivaroxaban depending on the genotype for SNP *CYP3A4* rs35599367. * Median $C_{max,ss}$ of rivaroxaban

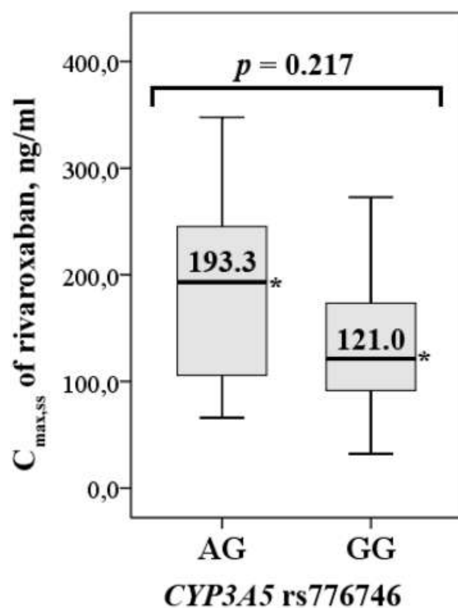

Fig. 4 Distribution of $C_{max,\ ss}$ of rivaroxaban depending on the genotype for SNP *CYP3A5* rs776746. *Median $C_{max,ss}$ of rivaroxaban

determined for *CYP3A5* rs776746 (A;G) and *CYP3A5* rs776746 (G;G) (p = 0.217; Fig. 4).

Further on, the influence of haplotypes on rivaroxaban $C_{max,ss}$ was assessed. Haplotype is the inheritance of a cluster of SNPs, which are variations at single positions in the DNA sequence individuals [10].

The patients were divided into the following haplotypes:

1. haplotype *ABCB1* rs1045642 (C;C) - *CYP3A4* rs35599367 (C;C) (wild-type haplotype 1) (n = 15),
2. haplotype *ABCB1* rs1045642 (C;T)—*ABCB1* rs1045642 (T;T)—*CYP3A4* rs35599367 (C;T) (mutant haplotype 2) (n = 4),
3. haplotype *ABCB1* rs4148738 (C;C)—*CYP3A4* rs35599367 (C;C) (wild-type haplotype 3) (n = 17),
4. haplotype *ABCB1* rs4148738 (C;T)—*ABCB1* rs4148738 (T;T)—*CYP3A4* rs35599367 (C;T) (mutant haplotype 4) (n = 3).

The analysis revealed no differences in rivaroxaban $C_{max,ss}$ between wild-type haplotype 1 and mutant haplotype 2, no significant differences in rivaroxaban $C_{max,ss}$ were found (p = 0.81; Fig. 5). There were also no significant differences in rivaroxaban $C_{max,ss}$ between wild-type haplotype 3 and mutant haplotype 4 (p = 0.842, Fig. 6).

Rivaroxaban $C_{max,ss}$ and PT2 correlation analysis revealed a statistically significant average correlation between these variables ($r = 0.421$; $r^2 = 0.178$; $p < 0.001$) (Fig. 7).

After a thromboprophylaxis course, 5 patients (6.4%) of 78 exhibited allergic, hemorrhagic, or thromboembolic complications (Table 4). Hemorrhagic complications resulted in nasal bleeding (n = 1; 1.28%) and hematoma in the postoperative wound area further complicated by infection (n = 1; 1.28%). Thromboembolic complications were PE (n = 1; 1.28%) and DVT (n = 1; 1.28%). One patient had an erythematous rash in the left elbow joint area.

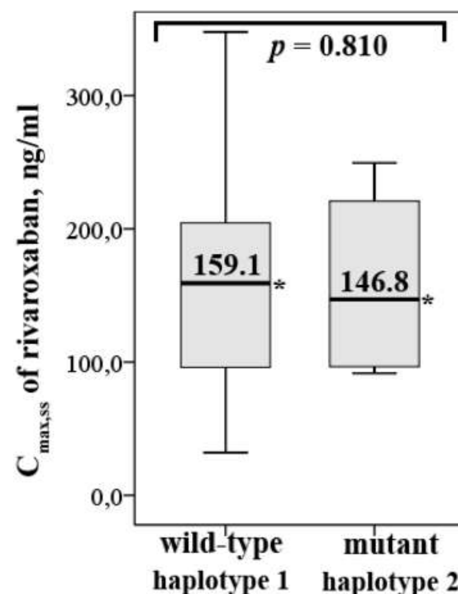

Fig. 5 Distribution of $C_{max,\ ss}$ of rivaroxaban depending on haplotypes. Explanation to haplotypes see in section Results. *Median $C_{max,ss}$ of rivaroxaban

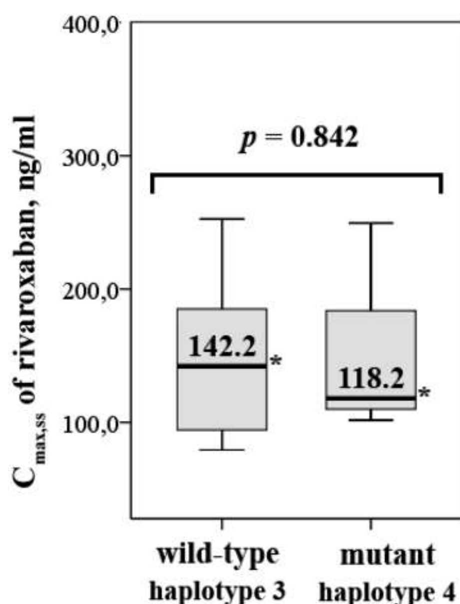

Fig. 6 Distribution of $C_{max,\ ss}$ of rivaroxaban depending on haplotypes. Explanation to haplotypes see in section Results. *Median $C_{max,ss}$ of rivaroxaban

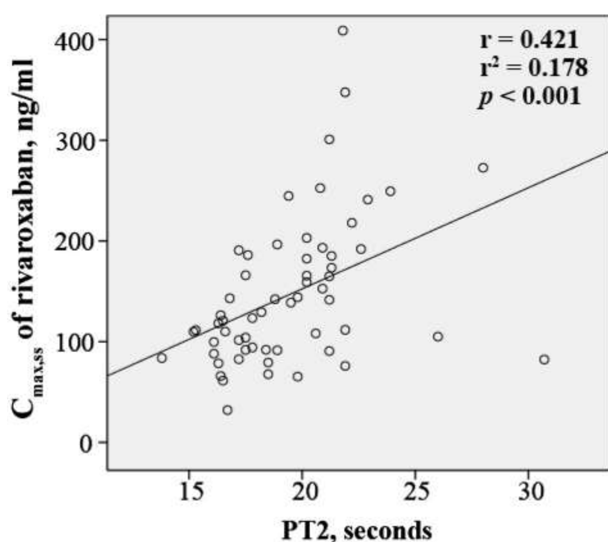

Fig. 7 Scatter chart, $C_{max,ss}$ of rivaroxaban and PT2 variables, THR and TKR patients

4 Discussion

Patients with mutant genotypes of studied SNPs did not show the expected increase in rivaroxaban concentration. The results of rivaroxaban $C_{max,ss}$ comparison between wild-type genotypes and mutant genotypes were not statistically significant. These results can be explained both by a small sample size and difficult pharmacokinetics of rivaroxaban. For example, dabigatran etexilate is a prodrug. The concentration of active form directly depends on carboxylesterase 1 (CES1). That is why dabigatran is easy for pharmacogenetics studies. Unlike rivaroxaban, which is metabolized by several CYP isoenzymes and excreted by several transporters. In this connection, it is advisable to conduct a haplotype analysis. In the real-life clinical practice, the search for a haplotype before including patients into the study is a challenge.

French researchers conducted a study that included 60 healthy male participants who were previously genotyped [11]. The goal of genotyping was to find if the participants carried haplotype *ABCB1* rs1045642—*ABCB1* rs2032582. The carriers of heterozygous haplotype showed an increase in the mean rivaroxaban $C_{max,ss}$ by 18%. An increase in the mean rivaroxaban $C_{max,ss}$ by 10.6% was found in carriers of the mutant homozygous haplotype. Unfortunately, the results were not statistically significant; because of a small sample, as explained by the researchers.

This haplotype analysis did not show a statistically significant difference between rivaroxaban $C_{max,ss}$ for wild haplotypes and mutant haplotypes. The small sample size puts limitations on the research.

Furthermore, PT was used to evaluate the anticoagulant activity of rivaroxaban. Earlier studies has close linear correlation between PT and concentration of anticoagulant in blood plasma [12, 13]. However, PT should not be converted to INR values, since INR was developed to normalize PT in patients receiving warfarin using the International Sensitivity Index (ISI).

This study revealed an average statistically significant linear correlation between rivaroxaban $C_{max,ss}$ and PT variables, despite the fact that rivaroxaban administration instructions indicate no need for anticoagulant activity monitoring. The results of this study suggest using PT, which is not expensive analysis, in clinical practice when there is a need to know rivaroxaban's anticoagulant activity (e.g., before urgent surgery).

Despite the good efficacy and safety of rivaroxaban, there are still factual cases of hemorrhagic and thromboembolic complications, in particular, registered nose bleeds (1.28%), hematoma in the surgical site (1.28%), PE, (1.28%) and DVT (1.28%). DVT and hematoma are consistent with the expected changes in rivaroxaban $C_{max,ss}$: it was increasing in the DVT patient and decreasing in the hematoma patient. Unfortunately, it is difficult still too soon to discuss the influence of the studied SNPs on rivaroxaban $C_{max,ss}$ with a number of observed outcomes, and there is a need to study all SNPs involved in rivaroxaban pharmacokinetics.

Table 4 Outcomes of rivaroxaban thromboprophylaxis in patients undergoing total hip and knee replacement surgery depending on genotype of studied SNPs *ABCB1* rs1045642, *ABCB1* rs4148738, *CYP3A4* rs35599367 and *CYP3A5* rs776746

Outcomes of rivaroxaban thromboprophylaxis	%	*ABCB1* rs1045642	*ABCB1* rs4148738	*CYP3A4* rs35599367	*CYP3A5* rs776746	Rivaroxaban $C_{max,ss}$, (ng/ml)
Erythematous rash in the area of the left elbow joint	1.28	C;C	T;T	C;C	G;G	141.6
Nasal bleeding	1.28	C;T	C;T	C;C	G;G	90.7
Hematoma in the postoperative wound area further complicated by infection	1.28	C;T	C;T	C;C	G;G	186.0
PE	1.28	C;T	C;T	C;C	G;G	166.0
DVT	1.28	T;T	C;C	C;C	G;G	79.3

5 Conclusions

A significant difference in peak steady-state rivaroxaban concentration between wild-types haplotypes and mutant haplotypes was not found. A larger sample is needed to show statistically significant results. It is advisable to assess the effect of the cluster of SNPs (haplotype) encoding metabolic isoenzymes and transport proteins on rivaroxaban $C_{max,ss}$. The prothrombin time analysis can be effective in clinical practice to assess the anticoagulant activity of rivaroxaban. In the future studies, it is advisable to include *CYP2J2* and *BCRP* genes into genotyping. Introduction of pharmacogenetic tests into a regular clinical practice will allow THR and TKR patients to avoid thromboembolic and hemorrhagic complications during rivaroxaban thromboprophylaxis.

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Compliance with Ethical Standards

Conflict of interest The authors have declared no conflict of interest.

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Affiliations

Dmitry Sychev[1] · **Radik Minnigulov**[2] · **Pavel Bochkov**[3] · **Kristina Ryzhikova**[4] · **Irina Yudina**[2] · **Aleksey Lychagin**[5] · **Tatyana Morozova**[6]

Dmitry Sychev
dimasychev@mail.ru
https://rmapo.ru/sveden/struct/13-rukovodstvo-akademii.html

Pavel Bochkov
bok-of@yandex.ru
https://rmapo.ru/science/nic/7330-otdel-personalizirovannoy-mediciny.html

Kristina Ryzhikova
kriistinkaa@mail.ru
https://rmapo.ru/science/nic/6402-sektor-molekulyarno-biologicheskih-issledovaniy.html

Irina Yudina
ikozlovskaya@mail.ru
https://www.sechenov.ru/univers/all/2034/

Aleksey Lychagin
dr.lychagin@mail.ru
https://www.sechenov.ru/univers/all/94952/

Tatyana Morozova
temorozova@gmail.com
https://www.sechenov.ru/univers/all/2912/

[1] Clinical Pharmacology and Therapy, Russian Medical Academy of Continuous Professional Education, 2/1 Barrikadnaya St., Moscow 123242, Russian Federation

[2] Department of Clinical Pharmacology and Propaedeutics of Internal Diseases, I.M. Sechenov First Moscow State Medical University (Sechenov University), 8-2 Trubetskaya St., Moscow 119991, Russian Federation

[3] Personalized Medicine Department, Research Center, Russian Medical Academy of Continuous Professional Education, 2/1 Barrikadnaya St., Moscow 123242, Russian Federation

[4] Department of Molecular Biological Research, Research Center, Russian Medical Academy of Continuous Professional Education, 2/1 Barrikadnaya St., Moscow 123242, Russian Federation

[5] Department of Traumatology, Orthopedics and Disaster Surgery, I.M. Sechenov First Moscow State Medical University (Sechenov University), 8-2 Trubetskaya St., Moscow 119991, Russian Federation

[6] Department of General Medical Practice, I.M. Sechenov First Moscow State Medical University (Sechenov University), 8-2 Trubetskaya St., Moscow 119991, Russian Federation