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POSSIBILITIES OF THE EFFICIENCY AND SAFETY CONTROL OF RIVAROXABAN APPLICATION IN PATIENTS WITH ATRIAL FIBRILLATION

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ABSTRACT: The results of a study of the concentration of rivaroxaban in the peripheral blood in patients with atrial fibrillation, receiving different doses of rivaroxaban, as well as in the case of developing hemorrhagic complications, are presented. 65 patients admitted for treatment for atrial fibrillation were examined. As an anticoagulant drug, rivaroxaban was prescribed at a dose of 15 or 20 mg once a day, depending on the state of renal function. The patients were divided into 3 groups depending on the prescribed dose of rivaroxaban and the presence or absence of hemorrhagic complications. At the same time, each patient underwent therapeutic drug monitoring of the drug. It was found that in patients, who received rivaroxaban at a dose of 15 mg, in 35% of cases its concentration in the blood was below the average minimum values. In patients, who received the drug at a dose of 20 mg, in 16% of cases its concentration in the blood serum exceeded the average maximum values. Patients treated with 15 mg of rivaroxaban lacked any hemorrhagic complications. In the group of patients with advanced hemorrhagic complications who received rivaroxaban at a dose of 20 mg, its serum concentration at all stages of therapeutic drug monitoring was significantly higher than the average maximum values and more than 4 times higher than in the control group (without hemorrhagic complications). The results of the study indicate the advisability of conducting therapeutic drug monitoring with the determination of rivaroxaban concentrations in the blood serum of patients receiving the drug, especially when they develop hemorrhagic complications.

Keywords: atrial fibrillation; new oral anticoagulants; rivaroxaban; pharmacokinetics; therapeutic drug monitoring; safety control.

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ВОЗМОЖНОСТИ КОНТРОЛЯ ЭФФЕКТИВНОСТИ И БЕЗОПАСНОСТИ ПРИМЕНЕНИЯ РИВАРОКСАБАНА У ПАЦИЕНТОВ, СТРАДАЮЩИХ ФИБРИЛЛЯЦИЕЙ ПРЕДСЕРДИЙ

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Резюме. Приведены результаты исследования концентрации ривароксабана в периферической крови у больных, страдающих фибрилляцией предсердий, получающих разные дозы ривароксабана, а также в случае развития у них геморрагических осложнений. Обследовано 65 больных, поступивших на лечение по поводу фибрилляции предсердий. В качестве антикоагулянтного препарата назначался ривароксабан в дозе 15 или 20 мг 1 раз в день в зависимости от состояния функции почек. Больные были распределены на 3 группы в зависимости от назначенной дозы ривароксабана и наличия или отсутствия геморрагических осложнений. При этом каждому пациенту проводили терапевтический лекарственный мониторинг препарата. Установлено, что у пациентов, получавших ривароксабан в дозе 15 мг, в 35% случаев его концентрация в крови была ниже средних минимальных значений. У пациентов, получавших препарат в дозе 20 мг, в 16% случаев его концентрация в сыворотке крови превышала средние максимальные значения. У больных, получавших 15 мг ривароксабана, отсутствовали какие-либо геморрагические осложнения. В группе больных с развившимися геморрагическими осложнениями, получавших ривароксабан в дозе 20 мг, его концентрация в сыворотке крови на всех этапах терапевтического лекарственного мониторинга была значительно выше средних максимальных значений и более чем в 4 раза превышала аналогичный показатель в контрольной группе (без геморрагических осложнений). Результаты исследования свидетельствуют о целесообразности проведения терапевтического лекарственного мониторинга с определением концентраций ривароксабана в сыворотке крови пациентов, получающих препарат, особенно при развитии у них геморрагических осложнений.

Ключевые слова: фибрилляция предсердий; новые оральные антикоагулянты; ривароксабан; фармакокинетика; терапевтический лекарственный мониторинг; контроль безопасности.

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BACKGROUND

Atrial fibrillation (AF) is currently the most common type of arrhythmia in cardiac patients, with a prevalence of up to 2% in the general population [1, 2]. AF significantly increases the risk of thromboembolic complications, particularly stroke, and nearly doubles mortality [3, 4]. The risk of ischemic stroke in patients with non-valvular AF is up to 5%, which is many times higher than in patients without AF [5, 6]. The most common cause of ischemic stroke as a thromboembolic complication, according to most researchers, is left atrial thrombosis [7–9]. The possibility of a stroke is only slightly affected by the type of AF, where a short paroxysm can result in thromboembolism [10].

In the presence of additional risk factors, AF patients take oral anticoagulants to prevent embolic stroke [11–14]. Previously, only warfarin, a vitamin K antagonist, was used for this purpose. According to R.G. Hart, L.A. Pearce, and M.I. Aguilar [15], timely administration of warfarin to AF patients significantly decreased the risk of stroke and lethal outcome. Unfortunately, warfarin has several drawbacks that severely limit its use. First and foremost, there is high variability in response to treatment in a specific patient, necessitating continuous monitoring of the international normalized ratio (INR). To address these shortcomings, new oral anticoagulants (NOA) have been developed and introduced into clinical practice [16]. Unlike warfarin, NOAs such as rivaroxaban, dabigatran, and apixaban have minimal individual variability in anticoagulant response, and the possibility of overdose is very low when renal function is taken into account [17]. At the same time, NOAs have several drawbacks. The main one is the possibility of hemorrhagic syndrome, which can progress to a hemorrhagic stroke. According to studies by J. Beyer-Westendorf, K. Foerster, S. Pannach, et al. [18], taking NOA resulted in significant bleeding in more than 7% of cases.

There are currently almost no reliable methods for monitoring the efficiency and safety of NOA use. Thus, prothrombin time (PT), a coagulogram indicator, may increase with rivaroxaban use. However, this indicator is practically useless at low drug concentrations in the blood. Furthermore, the indicators differ significantly when different thromboplastins are used as a reagent [17]. For these reasons, the INR indicator is also ineffective. Therefore, the use of activated partial thromboplastin time as a control, which increases while taking rivaroxaban, was expected. This indicator, on the other hand, has an extremely low sensitivity. In addition, there are currently no reliable standards for calibrating anti-Xa factor, the activity of which is affected by rivaroxaban [18].

Direct drug concentration determination in peripheral blood can be used as an objective method for monitoring the efficacy and safety of NOA. In this case, therapeutic drug monitoring (TDM) is most practical because it allows for dynamic monitoring of NOA concentrations in blood serum to select an individual dosing regimen for the drug. Currently, the average minimum and maximum NOA concentrations for various pathologies requiring anticoagulant therapy have been established [22]. Thus, the average minimum concentration of rivaroxaban (before taking the next pill) to prevent thrombogenesis in AF patients was 44 (12–137) ng/ml, and the average maximum concentration (3 hours after taking the pill) was 249 (184–343) ng/mL [20–22].

The study aims to investigate the rivaroxaban concentrations in peripheral blood in AF patients receiving different doses of rivaroxaban, as well as in the case of hemorrhagic complications.

MATERIALS AND METHODS

We studied 65 patients (34 men and 31 women, ages 53–85) admitted to the personalized medical center for AF treatment. Rivaroxaban was prescribed as an anticoagulant drug at a dose of 15 or 20 mg/day, depending on the presence of impaired renal function, upon admission. The patients were divided into three groups based on the rivaroxaban dose prescribed and the presence or absence of hemorrhagic complications (Table 1). At the same time, each patient was subjected to TDM.

The blood serum concentration of rivaroxaban was measured twice: before (test 1) and after (test 2) the drug was taken. GFR (glomerular filtration rate) was calculated using the CKD-EPI calculator to assess kidney function (GFR > 50 ml/min is considered normal).

For the quantitative determination of rivaroxaban in human serum, we used high-performance liquid chromatography

Table 1. Distribution of patients by groups
Таблица 1. Распределение больных по группам

Parameter	Group		
	1	2	3
Rivaroxaban, mg	15	20	20
Quantity	20	37	8
Age, years	76.6 ± 2.1	69.3 ± 1.3	68.3 ± 3.2
Gender, m/f	10/10	19/18	2/6

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with mass spectrometric detection, a selective, sensitive, and reproducible method. The internal standard method was used to perform quantitative determination calculations. The method's analytical range was 1–1000 ng/mL.

The data were statistically processed using the SPSS Statistics 22 software package and Microsoft Excel. The Student's t-test was used to compare the average data of independent samples. The significance level of difference was defined as a probability of at least 95% ($p < 0.05$).

RESULTS AND DISCUSSION

The concentrations of rivaroxaban in blood serum were compared in patients who received the drug at a daily dose of 15 mg (group 1) and 20 mg (group 2) during stage 1 of this study. There were no hemorrhagic complications in either group of patients. Rivaroxaban 15 mg was given to patients with a low GFR (< 50 ml/min). The minimum (point 1) and maximum (point 2) concentrations of rivaroxaban in group 1 administered with 15 mg of rivaroxaban, were approximately two times lower than in group 2, administered with a dose of 20 mg (Table 2).

At the same time, rivaroxaban blood concentrations were below the average minimum values (<12 ng/ml) in 35% of patients. Furthermore, when rivaroxaban was prescribed at a daily dose of 20 mg, the effective concentrations in 19% of patients were lower than the average minimum level for point 1. This may indirectly indicate rivaroxaban's insufficient efficacy in patients receiving it at a daily dose of 15 mg.

It was discovered that an excess of the maximum blood serum concentration of rivaroxaban (> 343 ng/ml) was observed in 16% of patients who received the drug at 20 mg. However, the excess of rivaroxaban was not detected in patients receiving the 15 mg. Thus, there was a risk of adverse drug reactions in patients receiving rivaroxaban at 20 mg.

During TDM, the concentrations of rivaroxaban in blood serum were compared in groups 2 and 3 of patients who received rivaroxaban at a daily dose of 20 mg (Table 3). There were no hemorrhagic complications in group 2. However, while taking rivaroxaban, eight patients of group 3 developed hemorrhagic complications. Hemorrhagic syndrome manifested itself in four of these patients as frequent development of subcutaneous hemorrhages, transient gross hematuria in three patients, and epistaxis in one case.

Table 3 shows that the blood serum concentration of rivaroxaban in group 3 patients who developed bleeding was 4.4 times higher at point 1 and 2.7 times higher at point 2 than in group 2. At the same time, all patients in group 3 had rivaroxaban blood concentrations higher than the maximum allowable levels at all stages of the examination. Hemorrhagic complications did not occur in patients receiving the 15 mg rivaroxaban.

In general, taking rivaroxaban at a daily dose of 20 mg causes a significant increase in blood concentration and the development of hemorrhagic complications much more frequently than taking it at a dose of 15 mg; because the rivaroxaban dose was prescribed strictly based on GFR, it can be assumed that this criterion does not fully meet the objectives. Therefore, TDM of rivaroxaban blood serum concentrations may be an option.

The sufficient and effective concentration of rivaroxaban in the blood is one of the objective criteria for the efficacy of prescribing it to patients. Thus, TDM should be greater than 12 ng/ml at point 1 (prior to the next rivaroxaban intake), and greater than 184 ng/ml at point 2 (3 hours after the drug intake).

At all stages of TDM, there was no excess of rivaroxaban concentration above the maximum allowable values among the patients who received it at a dose of 15 mg. Only 1.5% of those who received the drug at 20 mg and did not have hemorrhagic complications experienced an insignificant excess concentration. The blood concentration of rivaroxaban in the group of patients with hemorrhagic complications was significantly higher in all cases and five times higher than in group 2 (without hemorrhagic complications).

Table 2. Concentrations of rivaroxaban in blood serum (mg) in groups 1 and 2
Таблица 2. Концентрации ривароксабана в сыворотке крови в 1-й и 2-й группах, мг

Point	Group		*p*
	1	2	
1	26.5 ± 6.3	54.9 ± 18.5	0.153
2	115.6 ± 15.2	224.9 ± 30.1	0.002

Table 3. Serum rivaroxaban concentrations in groups 2 and 3
Таблица 3. Концентрации ривароксабана в сыворотке крови во 2-й и 3-й группах

Point	Group		*p*
	2	3	
1	54.9 ± 18.5	246.0 ± 75.4	0.01
2	224.9 ± 0.1	602.3 ± 61.5	0.000002

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As examples, consider the following clinical cases.

Patient Ya., 70, was admitted to the hospital after developing paroxysmal atrial flutter and complaining of rapid and irregular heartbeat and shortness of breath with moderate exercise. There were three points on the CHA2DS2-VASc scale and three on the HAS-BLED scale. During the patient's examination, the biochemical analysis of blood revealed a decrease in GFR (38 ml/min according to the CKD-EPI equation). Previously, the patient was prescribed rivaroxaban at 20 mg/day. Upon admission, gross hematuria was observed. TDM of rivaroxaban blood serum concentration was performed. The rivaroxaban concentration in sample 1 (taken immediately after the detection of gross hematuria) was 520.3 ng/ml, significantly higher than normal values. Therefore, the drug administration was discontinued. Rivaroxaban concentration was 121.69 ng/ml in repeated sampling 2 days after drug discontinuation. Gross hematuria was not observed after 4 days. Therefore, the rivaroxaban dose was reduced to 15 mg/day. Finally, the patient was discharged in good condition.

Patient L., 67, was admitted to the hospital with TDM. The patient had chronic lymphocytic leukemia and paroxysmal AF since 2009. There were three points on the CHA2DS2-VASc scale and three points on the HAS-BLED scale. The CKD-EPI equation calculated GFR to be 68 ml/min. The patient had previously been taking rivaroxaban at a dose of 20 mg/day. A hemorrhagic syndrome with manifestations in the form of subcutaneous hemorrhages was observed during the combined administration of an anticancer drug and rivaroxaban. TDM of rivaroxaban blood serum concentration was performed. The concentration of rivaroxaban in sample 1 was extremely high, measuring 436.92 ng/ml. The daily dose of the medication was reduced to 15 mg. The concentration of rivaroxaban was 284.08 ng/ml after repeated sampling. After three months, the patient returned for an appointment with no subcutaneous hemorrhages.

CONCLUSIONS

TDM of rivaroxaban concentrations in the blood of patients with AF revealed that in patients receiving rivaroxaban at a daily dose of 20 mg, its blood concentration was two times higher both prior to the next drug intake and three hours after administration than in patients receiving rivaroxaban at a dose of 15 mg.

The blood concentration of the drug was 4–5 times higher in the group of patients who developed hemorrhagic complications while taking 20 mg of rivaroxaban than in the group that did not develop hemorrhagic complications. The greatest difference was observed during blood sampling prior to the next rivaroxaban dose.

The blood concentration of the drug was very low in 35% of the patients studied, particularly those who received rivaroxaban at a dose of 15 mg, which could indicate insufficient efficacy of the drug at the indicated dose.

Given the lack of objective criteria for the efficacy and safety of NOA, particularly rivaroxaban, TDM with drug concentration determination in blood serum can be considered an effective method for monitoring therapy adequacy.

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