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Side effects and interactions with the use of rivaroxaban: Global pharmacovigilance data

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ABSTRACT

This study aimed to review literature data on the side effects and interactions when using rivaroxaban according to global pharmacovigilance data as of March 23, 2022. The data obtained are based on the VigiLyze expert-level analytical system and the use of the international VigiBase database of the WHO International Drug Monitoring Program.

Data processing and storage were performed using Microsoft Excel. The authors provided a consolidated expert opinion based on professional experience in clinical and scientific work. The received data contained 112,654 individual case safety reports (ICSR) about cases of adverse reactions to drugs, particularly rivaroxaban. When processing the ICSR database, duplicates and reports containing incomplete information that were not comparable with the Medical Dictionary for Regulatory Activities were excluded.

After processing, 32,779 ICSRs were extracted according to the criteria, which accounted for 29.1% of the total number of all ICSRs. Basic data on ICSR were recorded from the USA, Germany, France, Great Britain, and Japan. Most often, adverse reactions were observed in patients aged >75 years (31.9%), followed by patients aged 65–74 (20.0%) and 45–64 (15.3%). By age, more adverse reactions were observed in male (46.0%) patients. Countries that have developed pharmacomonitoring system contributed significantly to the development of the ICSR of the adverse reactions of rivaroxaban, namely, USA (*n*=62,992; 55.3%), Germany (*n*=9912; 8.8%), France (*n*=6983; 6.2%), Great Britain (*n*=5632; 5.0%), and Japan (*n*=5294; 4.7%). Adverse reactions were reported by 57.8% of ICSRs from medical and pharmaceutical professionals, including doctors, pharmacists, pharmacists, and other healthcare professionals. Adverse reactions with rivaroxaban include hospitalizations or its prolongation (47.8%), deaths (12.4%), and gastrointestinal bleeding (14.1%). Serious adverse reactions were observed in 99.4% of the cases. Drugs that were used in parallel or were not discontinued during the prescription of rivaroxaban were acetylsalicylic acid, clopidogrel, warfarin, and enoxaparin sodium. The risks of side effects increase when rivaroxaban is combined with other drugs, which must be taken into account when writing prescriptions.

Keywords: drugs; rivaroxaban; drug interactions; side effects; bleeding; safety; VigiBase.

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Нежелательные реакции и взаимодействия при применении ривароксабана: данные глобального фармаконадзора

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АННОТАЦИЯ

Проведён обзор литературных данных о нежелательных реакциях в ходе применения ривароксабана (по данным глобального фармаконадзора на 23 марта 2022 г.). Модуль для анализа данных VigiLyze обеспечивает глобальный сбор национальных данных о нежелательных явлениях, связанных с лекарствами и вакцинами, благодаря тесной интеграции с базой данных VigiBase (VigiLyze и VigiBase относятся к программам Всемирной организации здравоохранения по международному лекарственному мониторингу).

Обработку полученных данных и хранение осуществляли при помощи программы Microsoft Excel. Авторы консолидированно давали экспертное заключение, основываясь на профессиональном опыте клинической и научной работы. При анализе баз получено 112 654 индивидуальных сообщения о нежелательных реакциях (НР) (individual case safety report, ICSR) на лекарственные средства (ЛС). При обработке базы ICSR исключали дубликаты на одно и тоже сообщение, а также отчёты, содержащие неполную информацию, которые несопоставимы с Медицинским словарём для нормативно-правовой деятельности.

После обработки отобрано 32 779 ICSR — 29,1% от общего числа всех НР. Основные данные по ICSR были зафиксированы из США, Германии, Франции, Великобритании, Японии. Чаще всего НР наблюдались у пациентов в возрасте старше 75 лет (31,9%), у пациентов в возрасте 65–74 лет они отмечены в 20,0% случаев, в возрасте 45–64 лет — в 15,3% случаев соответственно. По возрасту больше НР отмечено у пациентов мужского пола (46,0%). Весомый вклад ICSR в изучение НР ривароксабана внесли государства, которые имеют развитую систему фармакомониторинга: США (62 992 случая; 55,3%), Германия (9912 случая; 8,8%), Франция (6983 случая; 6,2%), Великобритания (5632 случая; 5,0%), Япония (5294 случая; 4,7%). 57,8% ICSR о НР создано медицинскими и фармацевтическими работниками: врачами, провизорами и фармацевтами, а также другими профессионалами в сфере здравоохранения. В качестве НР при применении ривароксабана названы госпитализация или её продление (47,8%), на втором месте — летальные исходы (12,4%), а также желудочно-кишечные кровотечения (14,1%). Серьёзные НР отмечены в 99,4% случаев. На фоне назначения ривароксабана применялись параллельно или не отменялись следующие ЛС: ацетилсалициловая кислота, клопидогрел, варфарин, эноксапарин натрия. Риски возникновения НР увеличивались при комбинации ривароксабана с другими ЛС, что необходимо учитывать при назначении препаратов.

Ключевые слова: лекарственные средства; ривароксабан; лекарственное взаимодействие; нежелательные реакции; кровотечение; безопасность; VigiBase.

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BACKGROUND

Pharmacological treatment is crucial in maintaining and improving human health. However, the simultaneous use of several drugs and improper combination of drugs can increase the risk of adverse reactions (ARs) and result in the deterioration of the patient's condition. Moreover, even when using one drug, problems may arise in its combination with other drugs or food. Hence, the study of drug interactions is critical [1].

One of the drugs that require special attention when combined with other medicines is rivaroxaban, a widely used new-generation anticoagulant used to prevent and treat thrombosis and stroke [2]. Reliable data on its potential interactions with other drugs are required to prevent possible complications when using it. VigiBase, the global database of the Uppsala Monitoring Centre (UMC) of the World Health Organization Program for International Drug Monitoring (WHO PIDM) [3–5], can be used in this regard. It contains information on drug interactions and enables a qualitative analysis of the safety of the combined use of rivaroxaban with other drugs. The present review considered the main results of the study of drug interactions of rivaroxaban based on VigiBase data and recommendations for its combination with other drugs.

VigiBase as a support tool

The global VigiBase database is a valuable tool for healthcare professionals and pharmacists. It is a comprehensive collection of information on drugs and their potential interactions and contains data on thousands of drugs and information on ARs that may occur when two or more drugs are used simultaneously.

VigiBase is compiled based on spontaneous reports of drug interactions. This database was established by the World Health Organization in 1968 [4, 5]. It provides countries relevant data at a given time. Data analysis makes it possible to identify the risks of drug use and their interactions and is aimed at improving the quality and safety of drug therapy used in the healthcare system. When developing VigiBase, scientists extensively collected, analyzed, and systematized information on the effect of one drug on another [3–5]. Each record in the VigiBase database contains detailed information about the drug and its dosage, route of administration, and possible ARs. The user can obtain detailed results on the interaction of the selected drug with other drugs and make an informed choice in favor of safe and effective treatment based on this information [6].

VigiBase data is based on the results of clinical trials and publications in scientific journals. The database is constantly updated to present new research and discoveries in medicine, allowing specialists to be one step ahead and prevent possible problems associated with drug interactions.

Specialists can use VigiBase to assess potential risks when prescribing a combination of different drugs to one patient. Moreover, the database provides information on drug dosages that may need to be altered owing to potential interactions [3, 4].

Data from VigiBase can be used by doctors and pharmacists to make informed decisions about drug combinations and to prevent adverse drug interactions. This helps to improve the safety and efficiency of rivaroxaban treatment.

Analysis of rivaroxaban interactions with other medicines

In this section, we will review the main aspects of drug interactions of rivaroxaban based on data from VigiBase, and provide recommendations for the safe use of this drug. The results of clinical studies and publications and reports on ARs with the combined use of rivaroxaban with other drugs were studied and analyzed based on the global VigiBase database [7].

Some drugs may increase or decrease the efficiency of rivaroxaban. The cytochrome P450 3A4 inhibitor (ketoconazole) can increase its concentration in the blood, which may lead to increased pharmacological effect and risk of bleeding.

Moreover, some drugs may affect the metabolism of rivaroxaban and change its blood concentration. Cytochrome P-glycoprotein inducers (ramipril) [8, 9] can reduce the concentration of rivaroxaban, which may decrease its efficiency in preventing thromboembolic events.

However, most interactions of rivaroxaban with other drugs are moderate and manageable, and drug interactions can affect drug efficacy and safety. VigiBase provides valuable information on the possible interactions of rivaroxaban with other drugs.

The interaction of rivaroxaban with certain drugs may lead to a change in its pharmacokinetic or pharmacodynamic properties. For example, some anticoagulants, such as warfarin, can enhance the anticoagulant effect of rivaroxaban and increase bleeding risk; hence, when these drugs are used simultaneously, blood coagulation parameters should be carefully monitored.

Furthermore, some enzyme inhibitors or inducers were found to affect the formation of the active metabolite of rivaroxaban, and this can change its pharmacological action. In particular, a decrease in the activity of cytochrome P450 P3A4 can lead to increased concentration of rivaroxaban in the blood plasma and increased risk of adverse events [8, 9].

In recent years, several studies on rivaroxaban confirmed its efficiency and relative safety when used correctly. However, some factors that may affect the safety of this drug, especially in patients with certain conditions or when combined with other drugs, should be considered.

Several large studies have been conducted to evaluate the safety of rivaroxaban in different patient groups, namely, those who have undergone knee or hip replacement surgery or patients with atrial fibrillation.

One of the most significant studies was the phase III multicenter, double-blind, placebo-controlled ROCKET AF study, which included >14,000 patients with atrial fibrillation [10]. Rivaroxaban was randomly prescribed to the patients at a dose of 20 mg once daily (15 mg for patients with creatinine clearance of 30–49 ml/min) or warfarin. The key safety indicators, such as bleeding and other adverse effects, were assessed for a mean follow-up period of 1.9 years. The study showed that rivaroxaban is as safe as warfarin and has a lower risk of gastrointestinal bleeding [8, 9].

Another significant study, RECORD, assessed the safety of rivaroxaban after knee or hip replacement surgery. In this study, more than 9,000 patients received either10 mg of rivaroxaban once daily or 40 mg of enoxaparin once daily subcutaneously. The results showed that rivaroxaban was an effective and safe alternative drug for preventing thrombosis after surgery [11].

Additionally, other clinical trials, such as EINSTEIN DVT and EINSTEIN PE, were conducted, which assessed the safety and efficacy of rivaroxaban in the treatment of deep vein thrombosis and pulmonary embolism. Studies have shown that rivaroxaban is not inferior to alternative treatments, such as low-molecular-weight heparins with standard monitoring or fractionated heparin with selective monitoring [12].

The multicenter randomized MAGELLAN study compared the efficacy and safety of rivaroxaban and enoxaparin for the prevention of venous thromboembolism in patients hospitalized in severe condition. In this study, more than 8,000 patients received either 10 mg of rivaroxaban once a day or 40 mg of enoxaparin once a day subcutaneously. The results showed that rivaroxaban was effective and safe in the prevention of thrombosis in patients with acute diseases [13].

International experience of using rivaroxaban confirms its safety and efficacy in the treatment of various conditions in patients. Large clinical trials such as ROCKET AF, RECORD, EINSTEIN DVT, EINSTEIN PE, and MAGELLAN [11–13] have proven the absence of significant differences in the safety of rivaroxaban compared to other standard treatment methods. Rivaroxaban is a promising drug for a wide range of patients and, with proper administration and monitoring, can be used as an alternative to warfarin or heparins. The use of rivaroxaban should be considered worldwide.

A main problem with the use of anticoagulants is the probability of bleeding. Rivaroxaban, similar to other anticoagulants, can increase the risk of bleeding in patients. However, clinical trials have shown that this drug has a higher safety compared to the classic anticoagulant warfarin. In the ROCKET AF study, which included more than 14,000 patients, compared to warfarin, the use of rivaroxaban was associated with a lower incidence of bleeding, including intracranial and gastrointestinal bleeding [10].

Moreover, other clinical studies have confirmed the safety of rivaroxaban. In the EINSTEIN DVT study in patients with deep vein thrombosis, rivaroxaban was used as an effective and safe drug for prevention of thromboembolic complications. Similar results were obtained in other studies on large groups of patients [12].

Recommendations for managing drug interactions when using rivaroxaban

When using rivaroxaban, possible drug interactions with other drugs should be evaluated. Certain recommendations for managing these interactions should be followed to ensure the safety and effectiveness of treatment.

Before starting rivaroxaban therapy, a full examination of the patient should be conducted, and all drugs taken by the patient should be listed [14, 15]. This will eliminate the possibility of adverse interactions and allows for selecting the optimal dosage.

If the patient is taking any drugs that may interact with rivaroxaban, it is crucial to evaluate the potential benefit of the combination of these drugs and possible risks. In some cases, a dose adjustment or replacement of one of the drugs may be required.

Particular attention should be paid to such groups of drugs such as anticoagulants (including acetylsalicylic acid) [16] and antihypertensive, antiarrhythmic, and anti-inflammatory drugs. The interaction of rivaroxaban with these drugs may affect its efficiency or increase the risk of ARs.

This review aimed to analyze the main safety aspects of rivaroxaban use and ARs to the drug and its drug interactions according to the VigiBase database as of March 23, 2022.

VigiBase DATA ANALYSIS ON ADVERSE EFFECTS AND INTERACTIONS WHEN USING RIVAROXABAN

The data obtained are taken from the expert level analytical module VigiLyze, which is a tool of the international database VigiBase of UMC WHO PIDM. When analyzing the data, methodological approaches were used for processing the information obtained, which are accepted in the global pharmacovigilance system. This provides a generalized assessment of the received reports on all cases of ARs using individual messages (individual case safety report, ICSR) in VigiBase of UMC WHO PIDM in cases of using rivaroxaban as a recommended anticoagulant in various conditions. Open access to VigiBase (via the VigiAccess module) was used for a cross-assessment (with expert access) of ICSRs received from national pharmacovigilance centers of 92 WHO PIDM member countries that provided information on the safety of rivaroxaban use to the UMC. Search filters were used in the VigiBase ICSR system with queries on the use of rivaroxaban; a query was made in the program under the heading “rivaroxaban” and by the keywords *acidum acetylsalicylicum*,

clopidogrel, *warfarin*, and *enoxaparin sodium*. When processing the data, limitations were considered. The data obtained was processed and stored using Microsoft Excel. The authors provided a consolidated expert opinion based on their professional experience in clinical and scientific work.

RESULTS

As of March 23, 2022, 112,654 ICSRs on drug ARs containing information on rivaroxaban were received from the VigiBase database. When processing the ICSR database, duplicate messages and reports containing incomplete information that were not comparable with the Medical Dictionary for Regulatory Activities were excluded. After processing, 32,779 ICSRs were selected according to the criteria, respectively 29.1% of the total number of all ARs. The main ICSR data were recorded in the United States (62,992 cases; 55.3%), Germany (9912 cases; 8.8%), France (6983 cases; 6.2%), Great Britain (5632 cases; 5.0%), and Japan (5294 cases; 4.7%). Furthermore, 57.8% of ICSRs were generated by healthcare and pharmaceutical professionals, namely, physicians (36.2%), pharmacists and senior pharmacists (9.7%), and other healthcare professionals (11.9%). The reports demonstrated high quality of information. This is based on the pooled results of pharmacovigilance systems from different countries, indicating all information (accuracy, completeness), which fully satisfied the questionnaire requests. ARs were most frequently reported in patients aged >75 years (31.9%); in patients aged 65–74 years and 45–64 years, they were registered in 20.0% and 15.3% of cases, respectively. By age, more ARs were reported in male patients (46.0%). Table 1 presents data indicating the highest number of ICSRs (>3.0%) on ARs of rivaroxaban and on cases of ARs. All information was consolidated according to the classification of the Medical Dictionary for Regulatory Activities.

It is noteworthy that the data obtained and the assessment of the AR development when the use of rivaroxaban indicate the volumes of use of this drug on the market. Moreover, more frequent prescription of rivaroxaban increased the number of reports of ARs. The largest number of data is received from countries with developed pharmacovigilance systems (indicated above). The information obtained cannot be used to characterize the quality and efficiency of rivaroxaban, but can be a certain vector if the drug should be prescribed.

Serious ARs were noted in 99.4% of cases, with 12.4% being fatal. Table 2 shows the criteria for the severity of outcomes in the ICSR.

The reports indicate the drugs that were used simultaneously with rivaroxaban or were not canceled during its use. According to ICSR, acetylsalicylic acid was prescribed in 16.5%, clopidogrel in 3.3%, warfarin in 1.4%, and enoxaparin sodium in 0.8% of cases.

Table 1. The number of individual case safety reports and adverse reactions to rivaroxaban

Adverse reactions	*n* (%)
Gastrointestinal bleeding	22 368 (14.1)
Epistaxis	8614 (5.4)
Hemorrhage	7918 (5.0)
Hematuria	6055 (3.8)
Rectal hemorrhage	5703 (3.6)
Intracerebral hemorrhage	5076 (3.2)

Table 2. Severity criteria of outcomes in individual case safety reports

Severity criteria	%
Death	12.4
Threat to life	4.3
Hospitalization or its prolongation	47.8
Injury or disability	1.7
Other significant medical events	33.1

CONCLUSION

As of March 23, 2022, the VigiBase database contained 112,654 ICSRs for drugs, particularly rivaroxaban. According to the criteria, 32,779 ICSRs were subject to expert analysis, respectively 29.1% of the total number of all ARs. A significant contribution to the increase in the number of ICSRs on the development of ARs to rivaroxaban was made by countries with a developed pharmacomonitoring system, namely, the United States, Germany, France, Great Britain, and Japan. Medical and pharmaceutical workers, namely, doctors (36.2%), pharmacists and senior pharmacists (9.7%), and other healthcare professionals (11.9%), created 57.8% of ICSRs. ARs were most often noted in patients aged >75 years (31.9%), and were registered in 20.0% of patients aged 65–74 years and in 15.3% of patients aged 45–64 years and mainly in males (46.0%). ARs when using rivaroxaban included hospitalization or its prolongation (47.8%), followed by fatal outcomes (12.4%) and gastrointestinal bleeding (14.1%). Serious ARs were registered in 99.4% of cases. Medicines that were used concomitantly or were not canceled during the administration of rivaroxaban included acetylsalicylic acid, clopidogrel, warfarin, and enoxaparin sodium. The risks of ARs increased with a combination of rivaroxaban with other drugs, which should be assessed when prescribing the therapy.

ADDITIONAL INFORMATION

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