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Supratherapeutic International Normalized Ratio on Rivaroxaban and the Mechanisms behind it: A Systematic Review

Angela Khidhir DO MSc

Leonard Palatnic DO, Usman Najam DO University at Buffalo Jacobs School of Medicine and Biomedical Sciences, USA

ABSTRACT

Rivaroxaban is a direct oral anticoagulant that works by inhibiting factor Xa. There have been multiple reports of elevated international normalized ratio (INR) and incidents of bleeding in patients on rivaroxaban, which brings into question the potential need for monitoring. The purpose of this review is to differentiate the patients that may benefit from regular monitoring and to propose future directions for the implementation of monitoring. We conducted a systematic review of similar reports in the literature with the goal of identifying the factors that could influence rivaroxaban's levels in the blood or its influence on the INR. We reviewed PubMed using keywords including "rivaroxaban", "anti-Xa", "DOAC", "elevated", "INR", "bleeding", "hemorrhage", "pharmacology", and "pharmacokinetics". The literature revealed reports of INRs up to 5.2. Reviewing the pharmacokinetics of rivaroxaban indicated possibly higher drug levels in Caucasians, patients with a low body mass index (BMI), and patients with polymorphisms in the genes coding for CYP3A4, CYP2J2, or p-glycoprotein, assuming no renal or liver disease and no significant drug-drug or drug-food interactions. INR can be falsely normal if the thromboplastin reagent used to monitor the INR on warfarin is not sensitive to the changes in INR due to rivaroxaban. We suggest finding a thromboplastin reagent that is sensitive to INR changes with rivaroxaban, which could yield clinically relevant INRs on rivaroxaban allowing for accurate monitoring. We then suggest conducting studies to evaluate the cost-effectiveness of regular monitoring in at-risk patients.

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***Corresponding author**

Angela Khidhir, DO, MSc, Leonard Palatnic DO, Usman Najam DO University at Buffalo Jacobs School of Medicine and Biomedical Sciences, Buffalo NY, 14228, USA. E-mail: angelakh@buffalo.edu

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Abbreviations

International normalized ratio (INR), prothrombin time (PT), direct-acting oral anticoagulants (DOAC), deep vein thrombosis (DVT)

Introduction

Rivaroxaban (Xarelto®; produced by Bayer Pharma AG established in Berlin, Germany) is one of the relatively newly developed direct oral anticoagulant drugs (DOACs) developed to offset the disadvantages associated with direct vitamin K inhibitors (VKAs), including the frequent need for monitoring due to their variable pharmacokinetic profile and increased risk for hemorrhage [1, 2]. The list of indications for DOAC's use continues to expand. It includes treatment of recurrent deep venous thrombosis (DVT) and pulmonary embolism (PE), as well as, reducing the risk of stroke and systemic embolism of non-valvular atrial fibrillation [3].

Rivaroxaban has been shown to significantly reduce the incidence of acute limb ischemia, major amputation, myocardial infarction, ischemic stroke or death from cardiovascular causes in patients with peripheral vascular disease who have undergone lower-extremity revascularization at a dose of 2.5 mg BID when combined with aspirin [4].

Prothrombin time (PT) is the most commonly used laboratory value to test for coagulation [5]. PT value can vary between different laboratories based on the sensitivities of available thromboplastin agents to the reduction in coagulation factors. The International Normalized Ratio (INR) is used instead to correct for this variability, which makes it utilizable regardless of the reagent used. It is calculated mathematically by using the manufacturer's international sensitivity index (ISI), which is the ratio of the responsiveness of a particular thromboplastic agent to the reduction of coagulation factors relative to the primary World Health Organization international reference preparations [6].

The development of DOACs, including rivaroxaban, has negated the need for regular INR monitoring that is associated with VKAs. However, there have been multiple reports of elevated INR while on rivaroxaban that are occasionally clinically significant in the form of hemorrhaging, which raises the question of potential need for monitoring. The objective of this study is to conduct a systematic review of those reports in the literature with the goal of identifying the factors that could influence rivaroxaban's levels in the blood or its influence on the INR.

Methods

We reviewed PubMed using one or a combination of the following keywords; "rivaroxaban", "anti-Xa", "DOAC", "elevated", "INR", "bleeding", "hemorrhage", "pharmacology", and "pharmacokinetics". The resultant articles were thoroughly reviewed. A study is included if it provided INR values for patients on rivaroxaban or provided information on the pharmacokinetic or pharmacodynamic of the medication. All articles published in the English language published between 2010 and 2022 were included. PubMed was last searched on September 1st 2022. A study was excluded if it provided no report of the INR or did not provide any new information regarding the pharmacologic characteristics of rivaroxaban.

We extracted the INR values as well as any characteristics of the drug or laboratory process that could potentially influence rivaroxaban's levels in the blood or its influence on the INR was extracted. To avoid bias in excluding articles, all articles that included rivaroxaban in the title were thoroughly read.

In a multi-center registry-based study comparing rivaroxaban plasma level in patients with acute ischemic stroke and intracerebral hemorrhage, the highest INR reported was 4.6 [9]. Of note, in that study there was noted to be a correlation between plasma levels and INR, and that plasma levels were dependent on time since last intake, the dose, and renal function.

In a prospective multicenter study involving 20 volunteers studying the effects of rivaroxaban on commonly used point-of-care assays measuring hemostasis, rivaroxaban was found to mildly increase the INR by 0.32 (95% CI: 0.27 - 0.38) [10].

A case report noted an INR of > 8.0 in a patient mistakenly taking both warfarin and rivaroxaban 20 mg daily [11]. The patient had not experienced any signs or symptoms of bleeding. Five days after stopping rivaroxaban and reducing the dose of warfarin, the INR was found to be 4.3. Another case report described a supratherapeutic INR of 2.6 in an 88-year-old female with a history of atrial fibrillation treated with rivaroxaban 20 mg daily for eight months [12]. Of note, patient had been treated with amiodarone 3 weeks prior for an arrhythmia. Due to the elevated INR, the patient was referred to hematology, where rivaroxaban peak plasma concentrations were above the upper limit of detection (>800 μg/L). The patient's rivaroxaban was discontinued, and INR fell to 1.2 and plasma-rivaroxaban level to bethe low detection level (<25 μg/L) when measured 53 and 74 hours after the last rivaroxaban dose.

Discussion

Reviewing the pharmacology of rivaroxaban reveals that it has a relatively low molecular weight of 436g/mol. Rivaroxaban works by inhibiting free factor Xa (FXa), FXa bound to prothrombinase and FXa associated with a clot [13]. Per a scientific statement from the American Heart Association that summarizes the pharmacology of NOACs, levels of rivaroxaban peak in the blood in 2-4 hours [14]. It is 80-100% bioavailable at the 10-mg dose, and 66% bioavailable at the 20-mg dose. Bioavailability increases with food. It is highly protein bound, with 92-95% of it being bound to plasma protein. Volume of distribution is 50 L. The half-life is 5-9 hours in the general population but 11-13 hours in the elderly. About one third of it is hepatically cleared through oxidation by CYP3A4, CYP2J2, or hydrolyzed to inactive metabolites. It does not have any active circulating metabolites. It is a substrate of p-glycoprotein (P-gp) and ABCG2 (BCRP) [15]. In terms of excretion, 66% of it is renally excreted (36% as active metabolites and 33% as inactive metabolites). The remaining 28% is excreted in feces (7% as active metabolites, 30% as inactive metabolites).

Five studies and one case report were identified. A retrospective study in 2017 was done to assess the prevalence and extent of INR elevation in 218 hospitalized patients receiving rivaroxaban or apixaban as part of their home medications [6]. There was a statistically significant elevation of the INR above the upper limit of normal for both drugs (84% of patients on rivaroxaban and 78.3% of patients on apixaban).

Rivaroxaban was found to elevate the INR significantly more than apixaban, with the highest reported level being ~5.2 (median of 1.7 {IQR, 1.3–2.5} compared to a median of 1.4 {IQR, 1.2–1.6}; $P < 0.001$). However, no association was found between elevated INR and either age, sex, body mass index, the dose of DOAC (10, 15, 20 mg for rivaroxaban and 2.5 or 5 mg for apixaban), other comorbidities (27 conditions were tested), or other medications used on admission (50 drugs or drug classes were included). P-value was on the lower side (0.055) when the association with angiotensin II receptor blockers (ARBs) was studied (1.65 {1.31-2.22} in patients not on ARBs, vs 1.38 {1.25-2.05}). Aspirin therapy was associated with a lower INR (1.65 {1.3-2.33} compared to 1.44 {1.29-1.7}). No bleeding was reported in this study.

In a study investigating the factors influencing prothrombin time (PT) in patients with atrial fibrillation receiving rivaroxaban, 15 out of 69 patients (21.7%) had an INR > 1.5 [7]. However, the exact INR values were not reported. Interestingly, the patients that had INR > 1.5 had a lower incidence of stroke which indicates that the INR elevation on rivaroxaban is not always necessarily false.

In another study that modified a wet-chemistry point-of-care procedure to measure the concentrations of DOACs reported an INR range of 1.1 to 5.0 for rivaroxaban, but a range of 1.1 – 2.1 on dabigatran and apixaban [8].

Taking any medications or herbal supplements that induce or inhibit the previously mentioned clearance or excretion pathways can influence drug level. There has been reports on the effects of ARBs and ACEIs on blood coagulation and platelet function. Given that a good portion of patients on DOACs are likely also taking an ARB or an ACEI, the pharmacodynamic interaction should be better investigated. A study showed that about 37.8% of patients with an incident diagnosis of non-valvular AF at age 40 or greater who were taking DOACS were also taking ACEI/ARBs [16].

The International Sensitivity Index (ISI) used for warfarin cannot be reliably used to measure levels of rivaroxaban in vivo, however, there is a linear correlation between the two. This means that an elevated INR that is not accompanied by increased bleeding clinically may not be clinically significant [17].

Of all DOACs, rivaroxaban was found to affect PT and/or aPTT most reliably [17]. Therefore, there may be some potential benefit to routinely monitoring PT/INR while on the drug. There was a study that demonstrated a way for laboratories to locally calibrate their thromboplastin reagents to determine their own ISI, which could in turn make the INR sensitive to rivaroxaban's effects [17]. If a patient is actively bleeding or requiring surgical interventions, it may be useful to periodically assess their INR, similarly to warfarin. Alternatively, thromboplastin reagent manufacturers can

include two ISIs, one for rivaroxaban and one for warfarin. Using a rivaroxaban-specific normalized ratio was found to effectively minimize inter-thromboplastin variability [18]. It is also possible that in the future rivaroxaban levels can be monitored routinely instead. Studies should be done to assess the cost effectiveness of doing so. Two assays were found to be sensitive to detecting drug concentrations at peak levels but cannot precisely quantify it [10]. Alternatively, measuring the level of anti-Xa may be useful and the utility should be investigated [19].

We should also study the benefit of dose-adjustment based on BMI and age. Creatinine clearance is already advised to be taken into account when dosing for DVT or PE given that one third of the drug is eliminated unchanged by the kidneys [20, 21]. Studies can be done to better understand drug-drug interactions through the different pharmacokinetic mechanisms previously mentioned. If there is suspicion of metabolic interaction, the clinician may consider switching to edoxaban, which is minimally metabolized and exists primarily in an unchanged form in plasma.

Conclusion

Although rivaroxaban is widely used DOAC for different indications, it has been reported to be associated with elevated INRs in the literature and that elevation may be true and correlate with increased risk for bleeding. We explored different pharmacologic and non- pharmacologic explanations for this phenomenon. We suggest finding a thromboplastin reagent that is sensitive to INR changes with rivaroxaban, which could yield clinically relevant INRs on rivaroxaban allowing for accurate monitoring. We then suggest conducting studies to evaluate the cost effectiveness of regular monitoring in at-risk patients.

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