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Optimizing rivaroxaban therapy through therapeutic drug monitoring (TDM): A review article

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ABSTRACT

Therapeutic drug monitoring (TDM) is a technique used to measure and analyze plasma drug concentrations to optimize dosages for individual patients. The goal is to maintain drug concentration within target ranges to maximize therapeutic effects and prevent side effects. Rivaroxaban, a popular direct oral anticoagulant (DOAC) could cause risks such as drug interactions and bleeding. Therapeutic drug monitoring can help mitigate these risks by ensuring personalized and appropriate dosing for the individual patient. Within 2-4 hr after a dose, rivaroxaban reaches peak concentrations due to its rapid absorption with nearly perfect absorption at a 10 mg dose. Its pharmacodynamic effects are dose-dependent. There are no significant interactions between rivaroxaban and NSAIDs like naproxen or acetylsalicylic acid. Rivaroxaban exhibits potential for clinically significant interactions with drugs that inhibit CYP3A/P-gp pathways or possess antithrombotic properties. Notably, co-administration with strong P-gp/BCRP and CYP3A4 inhibitors, such as ketoconazole and ritonavir, can lead to a substantial increase in rivaroxaban exposure.

ABSTRAK

Therapeutic Drug Monitoring (TDM) adalah teknik mengukur dan menganalisis kadar obat dalam plasma untuk mengoptimalkan dosis pada pasien secara individu. Tujuannya adalah untuk mempertahankan kadar obat dalam kisaran target terapi sehingga dapat memaksimalkan efek terapi dan mencegah efek samping. Rivaroxaban, antikoagulan oral langsung (DOAC) yang dikenal luas, memiliki risiko seperti terjadinya interaksi obat dan pendarahan. TDM dapat membantu memitigasi risiko ini dengan memastikan dosis yang disesuaikan dan tepat untuk pasien secara individu. Rivaroxaban cepat diserap, mencapai konsentrasi puncak dalam 2-4 jam setelah pemberian dosis, dengan penyerapan hampir sempurna pada dosis 10 mg. Efek farmakodinamiknya bergantung dosis. Tidak ada interaksi yang signifikan antara rivaroxaban dan NSAID seperti naproksen atau asam asetilsalisilat. Namun, rivaroxaban dapat berinteraksi dengan obat-obatan seperti penghambat CYP3A/P-gp dan agen antitrombotik lainnya seperti enoxaparin atau warfarin. Pemberian bersamaan dengan penghambat CYP3A4 dan P-gp/BCRP yang kuat, seperti ketoconazole dan ritonavir, dapat meningkatkan paparan rivaroxaban secara signifikan.

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INTRODUCTION

Therapeutic drugs monitoring (TDM) is a way of measuring the plasma drugs concentration and knowing the interpretation.[1] It is one of those efforts to integrate the pharmacokinetics and pharmacodynamics, by measuring the drug concentration in plasma or other body fluids to optimize and individualized doses so that they are compatible with patients.[2] The main goal of TDM is to provide guidance in understanding unexpected reactions to long-term drug treatment, in addition to optimizing and tailoring dosage regimens to ensure effective and efficient drug therapy through maintaining drug concentration within the desired therapeutic range.[3]

The therapeutic window refers to the specific range of drug concentrations in the plasma that results in therapeutic effects with minimal risk of adverse or toxic effects for most patients. The main goal of TDM is to keep plasma drug concentrations within a predetermined range to improve treatment outcomes. Elevated concentrations are typically linked to a higher risk of adverse effects, while concentrations below the reference value suggest ineffective treatment or an unsatisfactory response.[4,5]

Measurements are usually performed on total drug levels in plasma, but in certain laboratories it is possible to determine levels of free drugs or even with samples from saliva. Some drugs may not indicate a correlation between the level of the drugs in the plasma with its therapeutic activities, in which monitoring is conducted to identify the possibility of the disorder in the drug intake. Therefore TDM is a guaranteed quality drug management system, which aims to deliver the right drugs, in appropriate patients, in the right doses, thus achieving the expected effects.[5]

Anticoagulants, commonly referred to as blood thinners, work to either stop blood clots from forming or stop them from getting bigger. These anticoagulant are crucial for the treatment and avoidance of illnesses linked to blood clots.[6] Based on their mode of administration and mode of action, anticoagulants can be categorized into several types 1) vitamin K antagonists (VKAs), which include warfarin, the most commonly used oral anticoagulant; 2) direct oral anticoagulant (DOAC), which includes dabigatran, apixaban, edoxaban, and rivaroxaban, which are novel oral anticoagulants that directly inhibit certain clotting factors, and 3) heparin and low molecular weight heparins (LMWHs) like enoxaparin and dalteparin, which are frequently used as intravenous anticoagulants that function by increasing the activity of thrombin III, a naturally occurring anticoagulant protein that inhibits thrombin and other clotting factors.[7,8]

Rivaroxaban is a new anticoagulant introduced to the market in recent years and is included in the class of oral anticoagulants (OACs) abbreviated as NOACs or DOACs. Initially, the drugs were named new oral anticoagulants, but the terminology changed over time to non-vitamin K antagonist oral anticoagulants and DOACs.[9,10] Rivaroxaban is an anticoagulant group that works directly by inhibiting blood clotting factors, which then becomes an alternative to warfarin and is increasingly used in clinical practice.[11] The use of DOACs has been authorized for the management and prophylaxis of thromboembolism, including deep vein thrombosis, particularly in its most severe manifestation, pulmonary embolism. Atrial fibrillation (AF) is the second most significant and critical indication for adult patients. Nowadays, the main drug used to prevent peripheral embolism and stroke is a DOAC. The first DOAC to be licensed for preventing the incidence of atherosclerotic in patients with a history of stroke, peripheral artery disease, or acute coronary syndrome was rivaroxaban.[12]

Before the DOAC was introduced, warfarin and other VKAs were the only OACs on the market. Unlike warfarin,

which requires regular monitoring, DOACs are approved without the need for regular monitoring. The DOACs are approved by the European Medicines Agency (EMA) for adult patients with the following therapeutic indication: stroke prevention and systemic embolism in AF, prevention/treatment of venous thromboembolism (VTE), pulmonary embolism (PE), and DVT/PE prevention in patients undergoing the knee or hip replacement surgery.[13,14]

The use of DOACs may give rise to several clinical concerns, including ambiguities about how drug interactions may affect drug concentrations, drug safety thresholds for major surgery, and the treatment of significant bleeding. Low anticoagulant concentrations are linked to thromboembolic events, whereas high amounts are linked to bleeding.[15] To learn more about the relationship between plasma concentrations, anticoagulant intensity, and clinical outcomes with this novel anticoagulant, studies on the pharmacokinetics-pharmacodynamics relationship of rivaroxaban are required. Furthermore, because of inter-patient variability, TDM might reduce the possibility of side effects related to these DOACs by customizing dosage.

DISCUSSION

Mechanism of action

In the prevention and treatment of VTE, factor Xa inhibitors are used. They are also utilized for preventing embolic disease in non-valvular AF and as an alternative anticoagulant in HIT. These drugs block factor Xa, the initial stage in the common pathway, through direct or indirect means. This inhibition is dose-dependent.[16] Apixaban and rivaroxaban attach directly to the active site of factor Xa, effectively preventing free factor Xa and the clot-associated form. Additionally, these drugs hinder prothrombinase activity.[17]

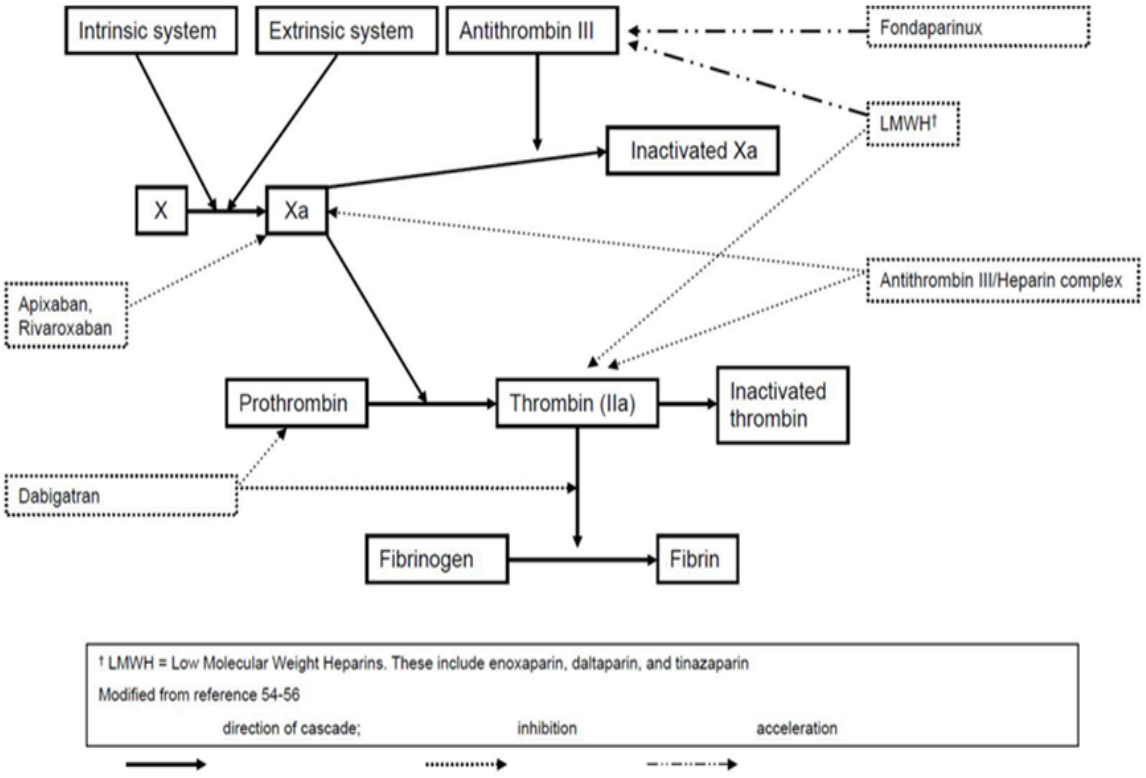


FIGURE 1. Mechanism of action of anticoagulant drugs: factor Xa inhibitors.[18]

Rivaroxaban does not require a cofactor to have an anticoagulant action, in contrast to indirect factor Xa inhibitors like fondaparinux.[11] In human plasma, rivaroxaban concentrations inhibit thrombin formation which thereby also inhibits the coagulation amplification process. At clinically relevant doses, rivaroxaban virtually totally inhibits the production of thrombi (80-100 nM).[19] Furthermore, by lowering thrombin, rivaroxaban enhances the permeability and degradability of the entire blood clot formation.[20] Rivaroxaban, however, does not stop the action of thrombin molecules that are already present.[21]

Pharmacokinetics

Direct oral anticoagulants are small synthetic molecules that are administered directly. They are rapidly absorbed in the bloodstream.[22] Rivaroxaban exhibits rapid absorption, reaching peak plasma concentration (C_{max}) within 2-4 hr following a single dose ranging from 1.25 to 80 mg or multiple doses up to 30 mg administered twice daily.[23]

Information from a different stage when rivaroxaban 20 mg tablets were co-administered with food, the absorption rate nearly reached perfection, boosting the AUC average by 39%, according to a study on healthy volunteers. Dose proportionality was attained under fed conditions with the administration of 10, 15, and 20 mg rivaroxaban tablets. Conversely, when rivaroxaban was administered with food at a dose of 20 mg, there was an increase in the mean AUC by 39%. The pharmacokinetics of rivaroxaban were not influenced by the type of food consumed (high-fat or high-carbohydrate).[24]

Studies on rats, rivaroxaban did not significantly cross the blood-brain barrier and was unevenly distributed to tissues and organs with only modest tissue affinity.[25] Human plasma protein has a high (92–95% *in vitro*) and reversible bonding with rivaroxaban. The primary plasma-binding ingredient is serum albumin.[22,26] As rivaroxaban binds to plasma proteins very well, dialyzability is anticipated. At steady condition, the distribution volume is roughly 50 L (0.62 L/kg), indicating a low to moderate affinity for peripheral tissues.[27]

Rivaroxaban is metabolised by several cytochrome P450 enzymes (CYP3A4/5, CYP2J2) and CYP-independent mechanism.[28] The following average values represent the contribution of these clearance pathways: of the overall amount of rivaroxaban eliminated, CYP3A4 contributes for around 18% and CYP2J2 for approximately 14%.[27] Urinary excretion eliminates 36% of the rivaroxaban dosage, with renal kidney secretion accounting for 30% and glomerular filtrating for 6%.[29]

With a terminal half-life of 5–9 hr in young, healthy subjects[21] and 11–13 hr in elderly subjects[30] rivaroxaban is eliminated from plasma. Healthy subjects have a systemic clearance of around 10 L/h (0.14 L/hr/kg) upon intravenous injection, with substantial inter-individual variability (coefficient of variation) ranging from 30 to 40%.[26,27,29]

In 2018, Sennesael *et al.*[31] investigated rivaroxaban levels in an emergency department patients experiencing bleeding incidents. They applied population pharmacokinetic modelling to estimate plasma concentrations at trough times and matched these against therapeutic ranges. The rivaroxaban levels measured in the patients ranged from 5 to 358 ng/mL, taken within 9 to 38 hr after sample collection. The estimated trough concentrations varied from 12 to 251 ng/mL, with a median of 94 ng/mL. Four patients were found to have unexpectedly high rivaroxaban levels. The factors identified for these high levels included inadequate dosing, excessive alcohol consumption, and lack of treatment reassessment.

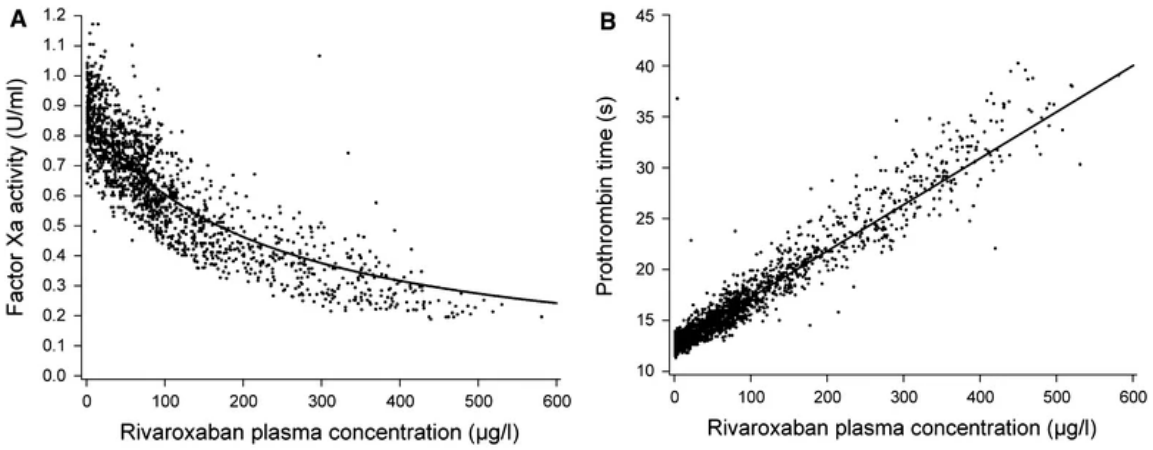
Additionally, half of the patients used drugs with potential pharmacokinetic interactions, and some took drugs that increased bleeding risk. Three genotyped patients have higher rivaroxaban levels

associated with specific SNPs. This study underscores the marked heterogeneity in rivaroxaban concentrations among emergency department patients. The findings highlight the potential utility of rapid DOAC measurements and PopPK modelling for individualized trough level prediction in this setting. Moreover, the authors advocate for the implementation of comprehensive follow-up programs, encompassing kidney function monitoring and evaluation for potential drug interactions, as a strategy to mitigate bleeding risk. Future studies could explore the development of clinically-implementable algorithms that integrate DOAC levels and PopPK modelling to optimize therapeutic management of patients on rivaroxaban presenting to the emergency departments.

Pharmacodynamic

Initial investigations in phase I trials revealed a dose-dependent inhibitory effect of rivaroxaban on factor Xa activity (FIGURW 2A).[23] Phase I studies revealed good tolerability and a lack of increased bleeding risk with single oral rivaroxaban doses up to 80 mg compared to placebo. This initial evaluation provided evidence of dose-dependent pharmacodynamic effects, manifested by suppression of factor Xa activity, prothrombin time (PT), and activated partial thromboplastin time (aPTT), along with HepTest prolongation. Notably, peak inhibition of factor Xa activity occurred within 1-4 hr post-administration, demonstrating selective targeting of this coagulation factor without affecting thrombin or antithrombin activity.[21] When multiple doses of up to 30 mg twice daily were administered, the inhibition of factor Xa activity was dose-dependent, peaking around 3 hr post-administration and persisting until the end of the dosing interval.[23]

The prolongation of PT (using neoplastin) showed a linear correlation with rivaroxaban plasma concentrations (FIGURE 2B) When tissue factor or collagen was stimulated, rivaroxaban (either a single 5 mg or 30 mg dosage) dose-dependently reduced the production of thrombin in healthy male participants. After a dose of 30 mg was given, several thrombin production characteristics were inhibited for a full day.[32]



FIGUURE 2. Concentration–effect relationship in healthy male patients receiving rivaroxaban for A) factor Xa activity, and B) prothrombin time.[27]

There is a variable degree of influence from demographic variables on the pharmacodynamic properties of rivaroxaban. After receiving a single 10 mg dose of rivaroxaban, older patients experienced greater suppression of factor Xa activity and longer PT than younger patients, however, these effects subsided within 24 hr.[33] Similar to the pharmacokinetics, differences in body weight, gender, and ethnicity have no discernible effect on the rivaroxaban pharmacodynamics.[33-36]

Rivaroxaban Interaction

The high bioavailability of rivaroxaban suggests that presystemic extraction, it is not important for absorption, such as via intestinal P-gp and CYP3A4. However, because P-gp/BCRP is involved in active renal secretion and CYP3A4 and CYP2J2 are involved in the oxidative metabolism of rivaroxaban. It is expected that co-administration of rivaroxaban with drugs that affect these pathways will affect the exposure levels of rivaroxaban in the body.[27]

Strong P-gp/BCRP and CYP3A4 inhibitors, such as ketoconazole and ritonavir, can greatly increase rivaroxaban exposure, according to a study on their co-administration. A single 10 mg dose of rivaroxaban given with 200 mg of ketoconazole daily produced a 1.8-fold increase in the AUC and a 1.5-fold increase in the C_{max} of rivaroxaban in phase I trials with healthy subjects. Coadministration of rivaroxaban, a commonly prescribed anticoagulant, with ketoconazole, an antifungal medication, significantly alters rivaroxaban pharmacokinetics. Studies have shown that concomitant daily use of rivaroxaban (10 mg) with ketoconazole (400 mg) leads to a substantial increase in systemic exposure, reflected by a 2.6-fold and 1.7-fold rise in AUC and C_{max}, respectively. Furthermore, steady-state ketoconazole treatment (600 mg twice daily) can elevate AUC by 2.5-fold following a single rivaroxaban dose (10 mg). These findings raise concerns about potential bleeding risk due to increased rivaroxaban exposure when co-administered with ketoconazole. The C_{max} was increased by a factor of 1.6 with ritonavir combined coadministration compared to alone administration. Rivaroxaban is contraindicated if administered concomitantly with strong inhibitors of CYP3A4 and P-gp because elevated serum levels will result, leading to potential bleeding.[27]

A phase I trial examined the pharmacokinetic interaction between rivaroxaban and enoxaparin, found no clinically significant relevant.[37,38] However, certain pharmacodynamic parameters of rivaroxaban activity increased by 50% when co-administered enoxaparin. Also, it had notable effects rivaroxaban was a significant anticoagulant. It showed increased efficacy. Further, studies found that this increase was consistent. More so in patients who needed both medications together. Yet the safety profile changed too. He observed higher anti-factor Xa levels caused different responses. Nevertheless, important to monitor patients closely due to these changes. Therefore combination therapy required caution.[38] Similarly, phase I trials assessing the interaction between warfarin and rivaroxaban reported no clinically significant pharmacokinetic differences. Nonetheless, during the transition period with rivaroxaban, the administration of warfarin affected pharmacodynamic parameters, showing prolonged PT values and higher INR additive values compared to when the drugs were given separately.[39]

In a study conducted by Kubitza *et al.*[34] in 2007, when rivaroxaban and naproxen, the most widely used NSAID, were combined, the bleeding time was much longer than when rivaroxaban was taken alone. However, on the other hand, the concurrent administration of both drugs only slightly affected rivaroxaban exposure (with rivaroxaban's AUC and C_{max} increasing by 10%). As a result,

the author came to the conclusion that rivaroxaban and naproxen did not significantly interact. Additionally, similar results were observed with rivaroxaban and acetylsalicylic acid. When both drugs were administered at the same time, rivaroxaban bled longer than when it was taken alone, but its pharmacokinetic properties stayed the same. Consequently, the authors came to the conclusion that there was no clinically meaningful interaction between rivaroxaban and ASA.[40]

CONCLUSION

Therapeutic drug monitoring plays a pivotal part in keeping up sedate concentrations inside helpful ranges, guaranteeing greatest viability while minimizing dangers such as dying or inadequately anticoagulation. Rivaroxaban shows quick retention, unsurprising pharmacokinetics, and dose-dependent pharmacodynamic impacts, with its action affected by components such as age, renal work, and concurrent medicines. Whereas intelligence with CYP3A4 and P-gp inhibitors, such as ketoconazole and ritonavir, can altogether increment dying dangers, no major pharmacokinetic intuitive have been watched with NSAIDs like naproxen or ibuprofen. The article emphasizes the esteem of TDM in giving personalized dosing methodologies to address personal inconsistency in reaction to rivaroxaban, eventually improving the security and viability of treatment. Also, it calls for assistance to inquire about and the execution of comprehensive follow-up programs to refine TDM conventions and way better coordinated them into clinical hone for DOACs. This approach underscores the potential of TDM in progressing personalized anticoagulant treatment and moving forward persistent results.

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