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How to Manage an Anticoagulated Patient in Case of Drug-Drug Interaction?

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Authors' contributions

Both authors designed, analyzed and interpreted and prepared the manuscript.

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Case Study

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ABSTRACT

Aims: The aim of this publication is to present the case of management of a patient on anticoagulation therapy with rivaroxoban in the context of a drug-drug interaction.
Presentation of Case: We report the case of a 73-year-old male diagnosed as having non-valvular atrial fibrillation treated with oral anticoagulants: dabigatran, acenocumarol and rivaroxaban in sequence.
Discussion: During concomitant administration of rivaroxaban and other commonly used agents, drug-drug interactions may occur. These can occur at the level of absorption, distribution, or clearance and are largely mediated by the P-gp transporter and the P450 (CYP) family of enzymes. One of the problems of direct-acting oral anticoagulants lies in the laboratory assays, as tests to measure drug levels are not well standardized and are not suitable for most centers. With rivaroxaban, PT is more sensitive than PTT; however, the results are dependent on the PT reagent used and other test with more specify have been introduced into the clinical practice.
Conclusion: It is pivotal that all clinicians who are treating patients with direct-acting oral anticoagulants become aware of relevant drug-drug interactions, as well as of the current limited possibilities to assess the level of anticoagulation.

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1. INTRODUCTION

Current guidelines recommend the use of oral anticoagulants (OAC) for a large number of indications. Among these indications are the prevention of venous thromboembolism (VTE) in patients with acute medical pathology in subjects undergoing orthopedic surgery or general surgery increased, also the use of OAC in the immediate treatment of deep vein thrombosis (DVT) is advised and pulmonary embolism (PE), as well as in the long-term prevention of thrombotic recurrence of both entities [1,2]. In addition the use of OAC is approved for long-term prevention of ischemic cerebrovascular disease in patients with atrial fibrillation (AF), as well as for the prevention of recurrent myocardial infarction in patients with acute coronary syndromes [3,4].

Currently, there are many options for anticoagulation: unfractionated heparin (UFH) or low molecular weight heparin (LMWH), OAC therapy with either vitamin K antagonists (VKA) or direct-acting oral anticoagulants (DOACs). All these drugs have demonstrated efficacy for treating venous thromboembolic disease, and to reduce the thrombotic risk [5]. However all of them have certain limitations. The main inconvenient of UFH and LMWH, are that must be administered parenterally. The AVK are drugs for oral administration; however, have a narrow therapeutic window, an unpredictable pharmacology, multiple interactions with food and gene regulation requiring frequent monitoring. The control of oral anticoagulant treatment is expensive and requires multiple dose adjustments to ensure that the anticoagulant effects are maintained within the therapeutic range. Some studies have shown that 50% of patients receiving warfarin are under or over-anticoagulation, implying that they are at risk of bleeding or thrombotic event [5].

DOACs have major pharmacologic advantages over VKA, including rapid onset/offset of action, less drug-drug interactions (DDIs), and predictable pharmacokinetics, eliminating the requirement for regular coagulation monitoring [6]. These new agents include the direct thrombin inhibitor dabigatran and the direct factor Xa inhibitors rivaroxaban, edoxaban and apixaban. However, because patients treated with the DOACs are not routinely monitored for changes in anticoagulation, practitioners must be aware of these agents' pharmacokinetic and pharmacodynamic profiles and DDIs [7,8].

Rivaroxaban is an oral direct FXa inhibitor (Table 1). This compound potently inhibits FXa with a 10 000-fold greater selectivity for FXa than for other related serine proteases, and effectively inhibits not only free FXa activity but also prothrombinase activity and clot-associated FXa activity [9-12].

Rivaroxaban also demonstrated a low propensity for clinically relevant drug– drug interactions with aspirin, the nonsteroidal anti-inflammatory drug, and the cardiac glycoside digoxin [10-12], which are potential concomitant medications in patients receiving anticoagulants for the prevention and treatment of thromboembolic disorders.

2. PRESENTATION OF CASE

This study was approved by the ethics committee of the University Hospital Fundación Jimenez Diaz. We report the case of a 73-year-old male diagnosed as having non-valvular AF and treated with oral anticoagulants. The patient had a history of hypertension, paroxysmal AF, sick sinus syndrome and pacemaker implantation, and was receiving concomitant treatment with rivaroxaban and rifampicin when he came to the anticoagulation unit. At this time, and following the recommendations of the EHRA practical guide [13] LMWH treatment was proposed, the therapy was refused by the patient.

In 2010 and due to his AF the patient started oral anticoagulant therapy with dabigatran prescribed by the cardiologist. In December 2012 the patient underwent knee-replacement surgery. In January 2013, he was hospitalized due to an acute infection of the prosthesis which was treated with levofloxacin 500 mg every 24 hours, amoxicillin 750 mg every 8 hours, and rifampicin 600 mg every 24 hours for 6 months. Additionally, dabigatran was replaced by acenocoumarol, due to the contraindication of concominant administration of rifampicin and dabigratan [13]. The patient developed a severe hypersensitivity reaction to acenocumarol consisting of in the arms and legs, and therefore the acenocoumarol was replaced with rivaroxaban in March 2013 (20 mg/24 hours). Finally, due to the persistence of the infection, the patient received 9 months of antibiotic treatment (levofloxacin 500 mg every 24 hours, amoxicillin 750 mg every 8 hours, and

rifampicin 600 mg every 24 hours). In 6 of the 9 months rifampicin and rivaroxaban were administered concomitantly. We must remember that according to EHRA guide on the use of DOACs in patients with non valvular AF interaction with rifampicin is greater in the case of dabigatran that rivaroxaban. The guide concluded that the use of dabigatran are contraindicated in concomitant administration with rifampicin; and in the case of rivaroxaban the practitioner have to consider dose reduction if another factor is present [13].

When the patient was attended for the first time in the anticoagulation unit we decided to perform periodic controls of anti-Xa activity, due to the interference of rivaroxaban with rifampicin, his refusal to receive parenteral anticoagulation and his hypersensitivity to acenocoumarol. The controls were scheduled every four weeks until the antibiotic treatment was completed (HemosIL Liquid Heparin Assay. IL. NY). Anti-Xa activity was measured two hours after ingestion of rivaroxaban. In adittion, controls of hepatic and renal function and coagulation profile, including prothrombin time (PT), were carried out (RecombiPlasTin 2G. IL. NY).

During six months of concomitant therapy with rivaroxaban and rifampicin, the patient did not develop complications related to anticoagulant treatment (thrombotic or haemorragic). Although we do not know the correlation between anti-Xa activity levels and the anticoagulant activity of rivaroxaban, levels of anti-Xa activity observed in the patient during the months of treatment were reduced compared to the levels obtained in other patients receiving rivaroxaban in our hospital (data not shown), who had no other concomitant treatments (Fig. 1). After discontinuation of rivaroxaban treatment, anti-Xa levels reached a similar value to levels in patients receiving rivaroxaban at the same doses [1.38 UI/ml (range 1.3-2.0 UI/ml)].

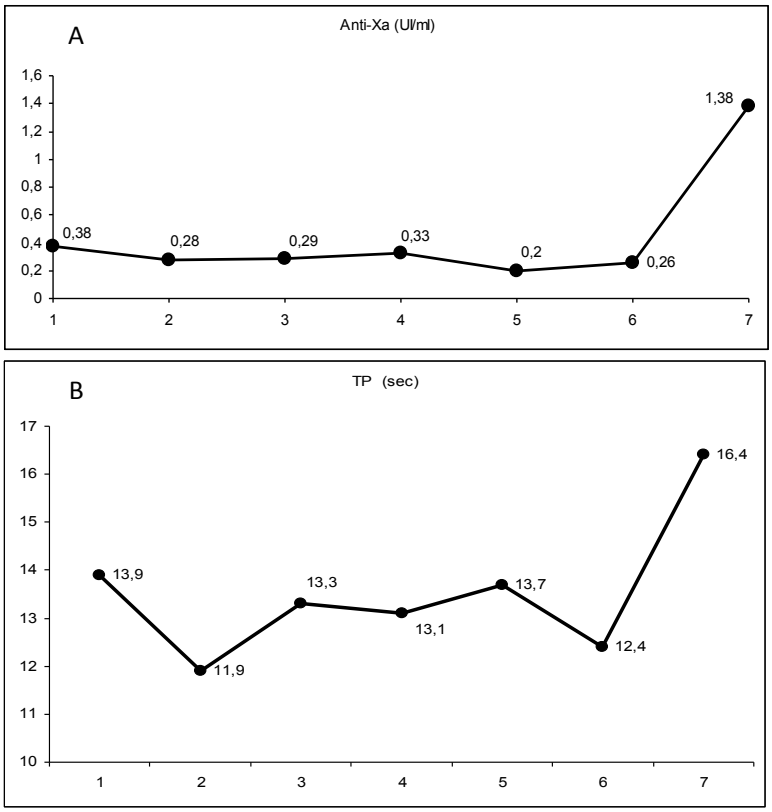

Fig. 1. A) Levels of anti Xa activity. Levels of anti-Xa activity observed during the months of treatment. After discontinuation of rivaroxaban treatment anti-Xa levels reached a similar value to levels in patients receiving rivaroxaban at the same doses (range 1.3-2.0 UI/ml). B) Levels of PT during the months of concomitant administration of rifampicin and rivaroxaban. The last value was obtained after the discontinuation of rivaroxaban treatment

Table 1. Pharmacologic properties of rivaroxaban

Property	Rivaroxaban
Dosing in AF	
CrCl >50 mL/min	20 mg once daily[a]
CrCl >30 mL/min	15 mg once daily[a]
CrCl 15-30 mL/min	15 mg once daily[a, b]
Mechanism of action	Direct factor Xa inhibitor
Prodrug	No
Protein binding (%)	92-95
Bioavailability (%)	~ 66
t_{max} (hours)	2-4
Route of elimination	36% renal (unchanged drug) 28% fecal/biliary (7% unchanged drug)
Metabolism	43% unchanged drug ~51% metabolites: - urine (30%) - feces (21%)
Half-life (hours)	5-9[c]
P-gp substrate	Yes
CYP substrate	Yes

Abbreviations: AF, atrial fibrillation; CrCl, creatinine clearance; P-gp, permeability glycoprotein; CYP, cytochrome P; t_{max}, time to reach maximum plasma concentration.

[a]Taken with the evening meal.

[b]Limited clinical data for patients with CrCl 15-29 mL/min.

[c]Increases to 11-13 hours in elderly subjects.

3. DISCUSSION

Rivaroxaban has relatively few drug interactions, but p-glycoprotein (P-gp) transporter inducers such as rifampicin may require dose adjustment because they reduce the drug's anticoagulant effect, and some guidelines advise to avoid the concomitant use [14]. However, we do not have the guidelines to adjust the dose correctly. Meanwhile, rivaroxaban administered in isolation has been found to have predictable pharmacokinetic profiles [8].

DDIs can occur at the level of absorption, distribution, or clearance and are largely mediated by the P-gp transporter and the P450 (CYP) family of enzymes [6]. CYP3A4 is present in largest quantity of all CYP enzymes in the liver and is involved in the oxidation of a vast array of chemically unrelated drugs from almost every drug class. Many DDIs result from the inhibition or induction of CYP enzymes involved in drug metabolism. CYP enzyme inhibition, and a resulting change in drug plasma levels, is the cause of much clinically important DDIs [15].

Rivaroxaban has a dual mode of elimination: approximately one-third of the drug is eliminated unchanged via the kidneys and two-thirds of the drug undergoes metabolic degradation in the liver, with half being excreted via the kidneys and half via the hepatobiliary route [15-18]. The multiple-pathway metabolism of rivaroxaban, which involves different classes of enzymes, should reduce the potential for CYP-mediated DDIs [17]. However, by inhibiting P-gp-mediated prevention of absorption, P-gp-mediated renal excretion, and CYP-mediated metabolism, drugs with combined P-gp and strong CYP3A4 inhibitory activity may significantly increase plasma rivaroxaban concentrations, leading to an increased risk of bleeding. By contrast, combined P-gp and strong CYP3A4 inducers could decrease rivaroxaban concentrations, consequently reducing the antithrombotic effect of rivaroxaban.

Co-administration of rivaroxaban and rifampicin, a potent inducer of CYP3A4, produced an approximate decrease of 50% in area under the curve, with parallel decreases in its pharmacodynamic effects [18-20]. Concomitant administration of strong CYP3A4 inducers must be made with caution in these circumstances; it may be wise to use any of the LMWH or VKA with careful INR control. In this case, the administration of VKA was not possible due to the hypersensitivity reaction developed after administration of acenocumarol, so the drug of choice should have been a LMWH.

One of the problems of DOACs lies in the laboratory assays, as tests to measure drug levels are not well standardized and are not suitable for most centers. With rivaroxaban, PT is more sensitive than PTT; however, the results are dependent on the PT reagent used and this test is not specific. Anti-factor Xa chromogenic assays with appropriate calibrators will provide sensitive and specific assays for measuring drug concentrations of oral direct factor Xa inhibitors [13]. In this case, the reduction observed on the anti-Xa activity is probably due to drug interactions of rivaroxaban with rifampicin.

It is pivotal that all clinicians who are treating patients with DOACs become aware of relevant DDIs, as well as of the current limited possibilities to assess the level of anticoagulation. This approach, proposed by Altera et al. [21] which involves spending resources to monitor patients treated with new anticoagulants, seems an effective solution to this problem.

We also believe that monitoring the anti Xa activity levels with the appropriated test in certain risk situations may be an appropriate method of preventing fatal events. However, it should be mentioned that this test is not easily available, especially in emergency setting, and has between-method variability. The test of PT has a good linearity and responsiveness. A recent publication of the Subcommittee of Control of Anticogulation of the International Society on Thrombosis and Haemostasis on the determination of the anticoagulant effect of rivaroxaban conclude that PT is the test of choice [22]. The report showed that the results depend on thromboplastin reagent used for testing, so the standarization across the reagents is necessary, and it can be feasible by employing an international sensivity index based on plasma supplemented with increasing doses of rivaroxaban [23].

4. CONCLUSION

DOACs levels will need to be interpreted in relation to timing of drug administration and the pharmacokinetics of the drug administered. Determination of the anticoagulant effect of rivaroxaban levels by anti-factor Xa quantitative calibrated assay may be useful in exceptional situations in which knowledge of rivaroxaban exposure can help in making clinical decisions. However, it would be necessary to know if the decreased anti-Xa activity levels corresponded with a decrease in drug action. Therefore, it is vitally important to closely monitor patients treated with rivaroxaban in certain circumstances, such as cases of renal failure, liver failure, and interactions with other drugs. This case illustrates one of the many possible situations that may occur in the real world due to the use of DOACs. Additionally, monitoring data from the use in real life of rivaroxaban may help to improve the management of this drug, especially in situations like the as described in this work, not included in clinical trials.

CONSENT

Consent was obtained from the patient for publication of this work.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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