Venous Thromboembolism Due to Suspected Interaction Between Rivaroxaban and Nevirapine

Duane Bates, Bruce Dalton, Janet Gilmour, and Jeff Kapler

INTRODUCTION

Rivaroxaban is a selective, reversible inhibitor of factor Xa that is used for the prevention and treatment of venous thromboembolism (VTE) and for the prevention of stroke in patients with atrial fibrillation. Nevirapine is a non-nucleoside reverse transcriptase inhibitor that is generally given in combination with 2 nucleoside reverse transcriptase inhibitors to suppress HIV in infected individuals. Both medications are metabolized in the liver through the cytochrome (CYP) P450 pathway. Nevirapine is also an enzyme inducer that may increase the clearance of rivaroxaban. There is a lack of information about drug interactions involving rivaroxaban after total joint replacement surgery. We report a case of VTE after total knee replacement that may have been due to an interaction between rivaroxaban and nevirapine.

CASE REPORT

A 60-year-old man was admitted to hospital for total knee replacement.* The patient’s medical history included hypertension, dyslipidemia, cerebrovascular accident of the right middle cerebral artery, osteoarthritis, post-herpetic neuralgia and polyneuropathy, and HIV infection. The HIV infection had been diagnosed 8 years before the current admission (viral load 270 000 copies/mL; CD4 nadir 0.266 × 10⁹/L [normal range 0.499 × 10⁹ to 1.651 × 10⁹/L]), but the patient had never had an AIDS-defining illness. The patient had no prior history of VTE and no known drug allergies. His body weight was 61.1 kg.

Medications before admission were nevirapine 400 mg daily, lamivudine 150 mg twice daily, zidovudine 300 mg twice daily, amlodipine 10 mg daily, metoprolol 50 mg twice daily, lisinopril 20 mg daily, hydrochlorothiazide 25 mg daily, atorvastatin 20 mg daily, acetylsalicylic acid 81 mg daily, celecoxib 200 mg daily, omeprazole 20 mg daily, gabapentin 300 mg 3 times daily, and lamotrigine 50 mg twice daily. The only change to the medication regimen in the past 2 years had been the discontinuation, about 3 weeks before admission, of abacavir 600 mg/lamivudine 300 mg because of intolerance and replacement with lamivudine 150 mg/zidovudine 300 mg.

At the time of the change in antiretroviral therapy, the patient had a viral load of less than 40 copies/mL and a CD4 count of 0.39 2 × 10⁹/L, which suggested a good virological response to therapy.

The patient received dalteparin 2500 units subcutaneously (SC) 6 h after the knee replacement surgery and then dalteparin 5000 units SC on postoperative days 1 and 2. Rivaroxaban 10 mg daily was started on postoperative day 3, at which time the patient was discharged from hospital; there were no other changes to the patient’s home medication regimen. At the time of discharge, the patient had no symptoms of VTE.

On postoperative day 4 (after 2 doses of rivaroxaban) the patient presented to the emergency department with shortness of breath, chest pain, and swelling of the left leg. He was hemodynamically stable, with oxygen saturation of 93% on room air and temperature 38.3°C. The only abnormalities noted on physical examination were a grade 2/6 systolic murmur and jugular venous pressure of 1–2 cm above the sternal angle. The left leg was warm and swollen, but no erythema or discharge was noted around the surgical site.

The results of laboratory tests at the time of this admission included hemoglobin 100 g/L (normal range 137–180 g/L), platelet count 139 × 10⁹/L (normal range 150 × 10⁹/L to 400 × 10⁹/L), white blood cell count 4.9 × 10⁹/L (normal range 4 × 10⁹/L to 11 × 10⁹/L), international normalized ratio (INR) 1 (normal range 0.9–1.1), activated partial thromboplastin time (APTT) 24.4 s (normal range 22–36 s), prothrombin time (PT) 12.1 s (normal range 10–13.5 s), INR 1 (normal range 0.9–1.1), activated partial thromboplastin time (APTT) 24.4 s (normal range 22–36 s), prothrombin time (PT) 12.1 s (normal range 10–13.5 s), international normalized ratio (INR) 1 (normal range 0.9–1.1), activated partial thromboplastin...
time 25.4 s (normal range 25–35 s), serum creatinine 107 μmol/L (normal range 50–120 μmol/L), and an estimated creatinine clearance of 57 ml/min (according to the Cockcroft–Gault formula). The results of liver function tests were total bilirubin 8 μmol/L (normal range 0–24 μmol/L), alanine aminotransferase 74 U/L (normal range 1–60 U/L), alkaline phosphatase 74 U/L (normal range 30–145 U/L), and γ-glutamyl transferase 15 U/L (normal range 11–63 U/L). Elevation of D-dimer (3.44 mg/L FEU [fibrinogen equivalent units]; normal range ≤ 0.46 mg/L FEU) and troponin T (21 ng/L; normal range 1–14 ng/L) were noted. Contrast-enhanced computed tomography of the lower legs and chest revealed a left-sided deep vein thrombosis (DVT) in the external iliac and common femoral veins, but the image was nondiagnostic for pulmonary embolism. There was no radiologic or clinical evidence of pneumonia. The results of blood, urine, and sputum culture were all negative. Electrocardiography displayed sinus tachycardia and lateral ST-T wave abnormalities.

In the emergency department, oxygen was started at 3 L/min, along with unfractionated heparin (80 unit/kg bolus, followed by infusion of 18 units/kg per hour) and warfarin. The rivaroxaban was stopped, and all other home medications were continued. On postoperative day 5, the heparin was switched to tinzaparin 10 700 units (175 units/kg) SC daily; at this point, the chest pain had resolved. On postoperative day 7, the oxygen was discontinued. As well, the only abnormality seen on transthoracic echocardiography was trace mitral regurgitation and trivial tricuspid regurgitation; the size and function of the left and right ventricles were normal. On postoperative day 9, the patient was discharged with prescriptions for warfarin (INR 3) and tinzaparin and was to be followed by Anticoagulation Management Services for INR monitoring. On postoperative day 10, the tinzaparin was discontinued (INR 2.5). On postoperative day 24 (INR 2.2), Anticoagulation Management Services transferred warfarin management to the family physician. The patient was stabilized with warfarin therapy as follows: 4 mg on Monday, Wednesday, Friday, and Saturday and 5 mg on Tuesday, Thursday, and Sunday.

DISCUSSION

Previous studies have shown that rivaroxaban is efficacious in preventing VTE after knee replacement surgery. Two randomized, double-blind studies, RECORD 3 (n = 2531 patients) and RECORD 4 (n = 3148 patients), compared enoxaparin 40 mg SC daily or enoxaparin 30 mg SC twice daily with rivaroxaban 10 mg daily after total knee replacement. In these trials, study medications were continued for 10–15 days, and patients were followed for 30–35 days. Mandatory bilateral venography was conducted between days 11 and 15. The primary outcome was a composite of DVT, nonfatal pulmonary embolism, or death from any cause during the treatment period. A modified intention-to-treat analysis was used in both studies and included patients who had undergone surgery, who took the study medication, and who had adequate assessment for thromboembolism. In the RECORD 3 trial, the modified intention-to-treat analysis (n = 1702 patients) revealed that the primary efficacy outcome occurred in 9.6% of the patients who received rivaroxaban and 18.9% of those who received enoxaparin (p < 0.001), which corresponded to an absolute risk reduction of 9.3% and a number needed to treat of 11. In the RECORD 4 study, the modified intention-to-treat analysis (n = 1924 patients) revealed that the primary efficacy outcome occurred in 6.9% of the patients taking rivaroxaban and 10.1% of those taking enoxaparin (p = 0.0118), which corresponded to an absolute risk reduction of 3.2% and a number needed to treat of 31. The incidence of major bleeding and non-major, clinically relevant bleeding was greatest in the rivaroxaban treatment arms, corresponding to an absolute risk increase of 0.64% and a number needed to harm of 156 (p = 0.039).

Unfortunately, the timing of VTE in the RECORD trials was not recorded, but venography was conducted between days 11 and 15. The risk of VTE is highest shortly after surgery, and the median time of diagnosis for thromboembolic events is 7 days after total knee replacement. The patient described in the current report presented with VTE 4 days after knee replacement surgery, and his VTE may have been related to an increased thromboembolic risk secondary to HIV infection and/or potentially enhanced clearance of rivaroxaban through a drug interaction with nevirapine.

A search of various drug interaction resources did not reveal any potential interactions between rivaroxaban and nevirapine. A review of Embase (January 1980 to December 2012), OVID (January 1946 to December 2012), International Pharmaceutical Abstracts (January 1970 to December 2012), and Reactions Weekly (January 1990 to December 2012) using the search terms “rivaroxaban” and “nevirapine” yielded no citations. Lexi-Interact 2012 listed nevirapine as a strong inducer of isozyme CYP3A4, suggesting that nevirapine may decrease the serum concentration of rivaroxaban. The severity was listed as major, and the reliability rating was fair. The references for this interaction were the Canadian and US product monographs. The area under the curve and maximum serum concentration for rivaroxaban were approximately 50% and 22% lower, respectively, when a single dose of the drug (20 mg) was administered to individuals who were also taking rifampin, a known strong inducer of isozyme CYP3A4 (titrated up to 600 mg/day). A similar statement appeared on the University of Liverpool website for interactions involving HIV drugs. In contradiction, another drug interaction reference suggested that nevirapine is a weak inducer of isozyme CYP3A4. The Drug Interaction Probability scale developed by
Horn and others’ suggests a possible drug interaction between nevirapine and rivaroxaban.

Treatment with drugs such as the rifamycins and some anticonvulsants (e.g., phenytoin, phenobarbital, carbamazepine) known to induce or up-regulate CYP enzymes predictably results in a marked reduction (by as much as 95%) in the plasma concentration of certain drugs administered concurrently. Furthermore, the anticoagulant effect of rivaroxaban correlates with plasma concentration. CYP3A activity is particularly sensitive to such modulation, and the metabolism of CYP3A substrates is affected by enzyme-inducing agents. Generally, the consequences of CYP3A induction do not appear immediately, since new protein must be synthesized. Steady-state levels are generally reached within 2–3 weeks. Metabolic induction dissipates slowly over a period of days to weeks, depending on the half-life of the inducer, the half-life of the CYP isozyme, the presence of hepatic disease, and the patient’s age. The patient described here had received nevirapine for years, so maximal enzyme induction of CYP3A4 was already present. The half-life of rivaroxaban is 5–13 h, so the patient’s plasma rivaroxaban levels potentially reached steady state within 48 h of starting rivaroxaban therapy.

Evaluation of the potential for an interaction between rivaroxaban and nevirapine relies on an understanding of the metabolism of the 2 drugs. Approximately two-thirds of rivaroxaban administered is metabolized to inactive metabolites and excreted in the urine and feces. The remaining third is excreted unchanged via the kidney. Approximately 30% of administered drug is metabolized via hydrolysis and oxidative degeneration catalyzed by CYP P450 isozymes 3A4, 3A5, and 2J2. In addition, rivaroxaban is a substrate of P-glycoprotein. Drug interactions involving both P-glycoprotein and CYP3A4 inducers or inhibitors are likely to be more substantial than those affecting either system alone.

Nevirapine undergoes extensive oxidative metabolism via the CYP system to several hydroxylated metabolites. The metabolism of nevirapine is mediated in part by the CYP3A4 and CYP2B6 isozymes; conversely, nevirapine also induces these isozymes by approximately 20% to 25%, which results in autoinduction of its own metabolism. In addition, nevirapine is an inducer of drugs metabolized by these isozymes, with maximal effect on CYP3A4 within 2–4 weeks after initiation of therapy. Autoinduction also results in a corresponding decrease in the plasma half-life of nevirapine, from approximately 45 h with a single dose to approximately 25–30 h following multiple daily dosing in adults. Nevirapine does not inhibit P-glycoprotein.

No information was found about increasing the dose of rivaroxaban if an enzyme-inducing agent is used concurrently. Phase II dose-finding studies of rivaroxaban after major orthopedic surgery did not support a dose–response relationship for the primary end point of any DVT, nonfatal pulmonary embolism, or death from any cause. A randomized, double-blind, double-dummy phase II dose-finding study (n = 621 patients) of oral rivaroxaban 2.5 mg, 5 mg, 10 mg, 20 mg, or 30 mg twice daily versus enoxaparin 30 mg SC twice daily after total knee replacement showed a significant increase in major bleeding with increasing dose (p = 0.0007).

One of the major dilemmas would be how best to monitor the effect of rivaroxaban, in order to balance the risks and the benefits, if the dose were increased for a patient receiving an enzyme-inducing medication. A chromogenic anti-Xa assay is the preferred test for monitoring rivaroxaban. In a quality control study, plasma samples were drawn from 20 healthy volunteers before and 2–3 h after a 10-mg oral dose of rivaroxaban and were analyzed with a chromogenic anti-Xa assay in 9 Swiss laboratories. The mean accuracy was 7% and the mean coefficient of variation for precision of rivaroxaban quantification was 8.8%. In randomized dose-ranging studies involving patients with normal renal function treated with approximately 22 mg of rivaroxaban daily for DVT, the mean maximum serum concentration (Cmax) 2–4 h after dosing was 270 µg/L (95% confidence interval [CI] approximately 160–400 µg/L) and the mean trough concentration (Cmin) was 25.5 µg/L (95% CI approximately 10–200 µg/L). Rivaroxaban plasma concentrations associated with increased risk of bleeding are not currently available.

The 2012 clinical practice guidelines of the American College of Chest Physicians list many treatment options for VTE prophylaxis in patients undergoing total knee arthroplasty, suggesting 10 to 14 days of treatment with either low-molecular-weight heparin, unfractionated heparin, fondaparinux, warfarin, apixaban, rivaroxaban, dabigatran, acetylsalicylic acid, or an intermittent pneumatic compression device. We are not aware of any clinicians using acetylsalicylic acid monotherapy to prevent VTE after orthopedic surgery. A low-molecular-weight heparin, fondaparinux, or unfractionated heparin could have been used for the patient described here and would not have interacted with his antiretroviral therapy. The patient was initially started on dalteparin 5000 units SC daily, which could have been continued for 10–14 days instead of being switched to rivaroxaban.

Warfarin is problematic because it interacts with many antiretroviral medications, such as non-nucleoside reverse transcriptase inhibitors, protease inhibitors, and the integrase inhibitor elvitegravir. Furthermore, empiric warfarin dosage adjustments are challenging because of limited clinical evidence and lack of pharmacokinetic studies. Therefore, the effect on INR response should be used to guide warfarin dosage requirements in patients receiving antiretrovirals.

Apixaban and dabigatran would have been the 2 remaining options for VTE prophylaxis in the patient described in this
case report. Approximately 15% of apixaban is metabolized via isozyme CYP3A4, compared with 30% for rivaroxaban. However, there is no information on the concurrent use of nevirapine and apixaban. The apixaban product monograph states that coadministration of apixaban with rifampin, a strong inducer of both isozyme CYP450 and P-glycoprotein, led to decreases of approximately 54% in mean apixaban area under the curve and approximately 42% in maximum concentration. These results suggest the potential for reduction in serum concentrations of apixaban and efficacy if combined with nevirapine. Given the lack of data, this combination cannot be recommended.

Dabigatran might have been a therapeutic option, as there were no clinically significant CYP P450 or P-glycoprotein drug interactions with the patient’s existing drug regimen. The patient’s creatinine clearance was 57 mL/min, which suggested no risk of dabigatran accumulation. Dabigatran was studied in the context of total knee replacement in the RE-MODEL trial (n = 2101 patients) and the RE-MOBILIZE trial (n = 2615 patients), both of which were randomized, double-blind, double-dummy, active-control non-inferiority studies. Oral dabigatran 150 mg or 220 mg daily was compared with enoxaparin 40 mg SC daily or 30 mg SC twice daily. Primary efficacy end points included total VTE events and all-cause mortality. Dabigatran was no less effective than enoxaparin 40 mg SC daily, but was inferior to enoxaparin 30 mg SC twice daily.

Many factors must be taken into account if a patient’s antiretroviral treatment is altered to accommodate other medical therapies. The aim of antiretroviral therapy continues to be maximal, lifelong, and continuous suppression of HIV replication to prevent emergence of resistance, to facilitate optimal immune recovery, and to improve health. The choice of regimen must consider convenience to the patient, tolerability, potential toxic effects, viral resistance, and drug interactions. In certain clinical scenarios, one or more agents in the regimen may be switched, as long as potency is maintained. Therapeutic drug monitoring is not recommended for general HIV care. However, it may be useful for pregnant women, children, and patients with renal or liver impairment, to minimize overexposure and adverse effects. In the case presented here, the patient was going to continue anticoagulation for a minimum of 6 months. He had had good virologic response to therapy in conjunction with one or more enzyme-inducing agents.

CONCLUSIONS

In the case reported here, a patient presented to hospital 24 h after discharge (following an admission for total knee replacement) with DVT and clinical signs of pulmonary embolism, specifically dyspnea, electrocardiographic changes, and elevated troponin T. Postoperatively and before the readmission, the patient had received a short course of dalteparin followed by 2 doses of rivaroxaban 10 mg daily. Although the patient’s HIV-positive status may have been a factor in the early presentation of VTE, concurrent nevirapine may have further increased the elevated hepatic clearance of rivaroxaban through induction of isozyme CYP3A4, leading to subtherapeutic anticoagulation. To the authors’ knowledge, this is the first report of a potential drug interaction between nevirapine and rivaroxaban. Clinicians should consider the potential ramifications of enhanced clearance of rivaroxaban when this drug is used in conjunction with one or more enzyme-inducing agents.

References

24. Duane Bates, BScPharm, ACRP, is a Clinical Practice Leader, Medicine, in the Department of Pharmacy, Foothills Medical Centre, Alberta Health Services, Calgary, Alberta.
25. Bruce Dalton, BScPharm, PharmD, is a Clinical Practice Leader, Infectious Disease, in the Department of Pharmacy, Foothills Medical Centre, Alberta Health Services, Calgary, Alberta.
26. Janet Gilmour, MD, FRCP, is Staff Physician in Internal Medicine, Department of Medicine, Foothills Medical Centre, Alberta Health Services, Calgary, Alberta.
27. Jeff Kapler, BScPharm, is a Clinical Pharmacist in the Southern Alberta HIV/AIDS Clinic, Alberta Health Services, Calgary, Alberta.

Duane Bates, BScPharm, ACRP, is a Clinical Practice Leader, Medicine, in the Department of Pharmacy, Foothills Medical Centre, Alberta Health Services, Calgary, Alberta.

Bruce Dalton, BScPharm, PharmD, is a Clinical Practice Leader, Infectious Disease, in the Department of Pharmacy, Foothills Medical Centre, Alberta Health Services, Calgary, Alberta.

Janet Gilmour, MD, FRCP, is Staff Physician in Internal Medicine, Department of Medicine, Foothills Medical Centre, Alberta Health Services, Calgary, Alberta.

Jeff Kapler, BScPharm, is a Clinical Pharmacist in the Southern Alberta HIV/AIDS Clinic, Alberta Health Services, Calgary, Alberta.

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Address correspondence to:
Duane Bates
Department of Pharmacy, Alberta Health Services
Foothills Medical Centre
1403 29th Street NW
Calgary AB T2N 2T9
e-mail: duane.bates@albertahealthservices.ca