

Medication error when switching from warfarin to rivaroxaban leading to spontaneous large ecchymosis of the abdominal and chest wall

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Abstract

Non-vitamin K oral anticoagulant (NOAC) therapy may be inappropriate if prescription was incorrect, the patient's physiological parameters change, or interacting concomitant medications are erroneously added. The aim of this report was to illustrate inappropriate NOAC prescription in a 78-year-old woman with non-valvular atrial fibrillation and borderline renal dysfunction who was switched from warfarin to rivaroxaban and subsequently developed bruising with hemorrhagic shock and acute on chronic renal failure. Administration of 4-factor prothrombin complex concentrate effectively reversed coagulopathy and stopped bleeding. Retrospective determination of circulating plasma levels of rivaroxaban and warfarin confirmed that excessive anticoagulation was likely due to warfarin that the patient probably continued to take although rivaroxaban was initiated. Pharmacodynamic interaction between rivaroxaban and warfarin may not only be additive but synergistic. In patients at high risk of complications, judicious prescribing and dosing of NOACs, and regular monitoring of concomitant medications and renal function are highly recommended.

Introduction

Extravasation from surrounding vessels of blood beneath the skin (ecchymosis or bruising) can result from abnormalities affecting the coagulation cascade function.¹ Bruises appearing on the trunk should raise one's suspicion of an underlying bleeding disorder, and

anticoagulants are among the most frequently seen causes of medication-associated bruising in the elderly. Older patients may be at additional increased risk of bruising from poor tissue turgor.²

Anticoagulants are often prescribed for prevention of systemic embolism or stroke in elderly patients with non-valvular atrial fibrillation (AF), which is the most common sustained arrhythmia, increasing in prevalence with age, reaching about 20% in those over 85 years old.³ Anticoagulants are recommended in patients with AF aged 75 years or above after assessing the bleeding risk with scores. Despite the significant reduction in stroke risk with the use of anticoagulants,⁴ it is the risk of bleeding, which partly explains the theoretical underuse of oral anticoagulation (OAC) in the elderly. The incidence of major bleeding related to vitamin K antagonists (VKA) may be as high as 13% per year.⁵

Rivaroxaban (RXN), a direct factor Xa (FXa) inhibitor, is a non-vitamin K oral anticoagulant (NOAC) available for therapeutic treatment over the last few years for several indications including thromboembolic disease and for the prevention of embolic events. Among patients with AF who were at moderate to high risk of stroke, RXN was compared with VKA in a randomized trial that included 14,264 patients with a median age of 73 years. The study results demonstrated that for the prevention of stroke or embolism, RXN was non-inferior to VKA, and fatal and intracranial bleeding occurred less frequently in the RXN group.⁶ In many countries, RXN has been approved for stroke prevention on the basis of this study results, however, important issues are not or poorly clarified like therapeutic drug monitoring, drug-drug interactions, switching between anticoagulant regimens, use in patients with chronic renal failure, and availability of an antidote. Therefore, in some countries NOACs will only be indicated if prothrombin time (PT) international normalized ratio (INR) control under VKA has been shown to be suboptimal, *i.e.*, time in the therapeutic range <65%.⁷ Strategies have been proposed for each of the therapeutic limitations in consensus guideline recommendations,⁷ however, randomized trials are required to validate many of them.

A case of lateral chest and abdominal wall bruising is presented here that illustrates several aspects associated with use of NOAC in AF in a real world setting.

Case Report

A 78-year-old Caucasian woman was admitted to the internal medicine ward of the Central Hospital of Bolzano (Bolzano, Italy) on November 7, 2015, after she was found by her

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daughter at home on the bedroom floor unable to get up. She was awake and oriented but could not tell what happened. Her past medical history included arterial hypertension, left ventricular hypertrophy with normal left ventricular function, dyslipidemia, and overweight (body mass index of 29 kg/m²). Around the age of 65, she had been occasionally seen in the hospital's outpatient department because of palpitations, when intermittent non-valvular AF had been diagnosed and successfully treated with amiodarone for a total of 3 years. Amiodarone was then suspended by her cardiologist. Long-term pharmacological treatment included daily aspirin 100 mg, nebivolone 5 mg, losartan 50 mg and hydrochlorothiazide 12.5 mg.

One month prior to admission, on October 8, 2015, she had been hospitalized for a first time because of chest pain in the presence of tachyarrhythmia. It was interpreted as a recurrence of non-valvular AF in congestive heart failure with bilateral pleural effusions and a moderately elevated N-terminal pro brain-type natriuretic peptide value of 4136 pg/mL. Acute coronary syndrome had been successfully ruled out, however, repeatedly elevated fasting blood glucose levels and an elevated glycated hemoglobin A1c level established the diagnosis of type 2 diabetes, for which dietary treatment was initiated. Tachycardia was successfully controlled by the reimplementation of amiodarone, which the patient had already well tolerated in the past; diuretic therapy was started with furosemide. Liver function parameters had been normal but creatinine levels were increased to 1.51 mg/dL corresponding to

a glomerular filtration rate (GFR) estimate of 32 mL per minute per 1.73 m² according to the *modification of diet in renal disease* (MDRD) formula. Because of AF, stroke and bleeding risks were scored with the results for CHA₂DS₂-VASc of 6 and for HAS-BLED of 3, respectively. Therefore, OAC with warfarin was started. The patient was discharged from hospital on October 21, 2015, when the PT INR value was within the therapeutic range of 2.0 to 3.0. A cardiology follow-up appointment was arranged for two weeks later, on November 3, 2015.

At the cardiologic follow-up, the patient felt well and there were no signs of heart failure. An electrocardiogram confirmed sinus rhythm, but with phases of atrioventricular type 2 block 2:1 characterized by intermittently non-conducted P waves. As the patient was on drug treatment with 200 mg of amiodarone and 200 mg of metoprolol divided in two doses, metoprolol was suspended. The patient furthermore reported to have already suspended OAC 2-3 days after discharge from hospital, as she could not physically present for regular coagulation checks due to orthopedic problems. Therefore, based on recent renal function parameter results that had been obtained when being discharged from the hospital, reduced dose RXN of 15 mg daily was started, notably without confirming normalization of PT INR.

Upon arrival in the emergency room, the patient had a normal Glasgow scale score of 15 points, arterial blood pressure was 60/40 and heart rate irregular at about 140 per minute. Body temperature was 34.5°C. Dark blue- to black-colored bruising was seen on the right lateral abdominal and chest wall as well as on the right upper extremity; she was without pain upon palpation of the abdominal wall, however, she stated that she had a painful chest and cervical spine. Radiographically bone fractures were excluded and cranial and cervical computerized tomography were also unremarkable. Hemorrhagic shock was confirmed by a hemoglobin value of 6 g/dL, a hematocrit of 20.6% and an arterial lactate of 6.7 mmol/L; she was anuric and her creatinine level increased to 5.55 mg/dL with normal serum calcium and phosphate levels. A concomitantly increased highly sensitive cardiac troponin T value of 162 ng/L was without kinetics on follow-up making acute coronary syndrome unlikely. NTproBNP level was increased to 13,600 pg/mL and blood glucose was 268 mg/dL.

Volume resuscitation was immediately initiated by rapid infusion of 500 mL of 0.9% sodium chloride followed by infusion of 150 mL of 0.9% sodium chloride per hour as the patient was fluid responsive and demonstrated a steady increase of arterial blood pressure. Two units of packed red blood cells (PRBC) were

also given. After 6 h of therapy, she was hemodynamically stabilized. Three more units of PRBC were administered up to day 2 as hemoglobin levels had remained below 7.5 g/dL. Urine production returned with volume resuscitation on day 1, however, severe coagulopathy remained unchanged until day 2 despite presumed pharmacokinetic reduction in circulating RXN levels over time. This observation, in combination with the notion that in the literature a INR value as high as the one seen in this patient had never been reported with RXN overdose, 3500 U of 4-factor prothrombin complex concentrate (PCC) (Confidex®; CSL Behring, Milano, Italy) in combination with intravenous administration of 5 mg of vitamin K were administered on day 3. This treatment was also given because the hemoglobin value did not further increase on day 3 despite administration of 2 more units of PRBC, which might have been due to ongoing bleeding resulting from ongoing coagulopathy. PCC and vitamin K administration immediately reversed highly elevated INR to a value of 1.7, thus, confirming vitamin K-dependent clotting factor deficit rather than RXN overdose.

Additional anamnestic exploration after clinical stabilization of the patient failed to clarify anticoagulant adherence. The patient confirmed initiation of the newly prescribed blood thinning medication but could not confirm cessation of warfarin therapy. In order to retrospectively deconvolute the clinical presentation, effective plasma levels of RXN and warfarin were determined in conserved blood samples from days 1, 3 and 4. As shown in Table 1, RXN was detected on day 1 but levels were low, and were below the lower limit of detection on days 3 and 4; warfarin, in contrast, was detected on days 1, 3 and 4 at therapeutic doses, thus, confirming that the patient had continued to also take the VKA-based OAC.

The rest of the clinical course was unremarkable. By the end of day 3 the patient became polyuric and subsequently returned to her previous renal function. On days 5 and 6, one additional unit of PRBC was given, respectively, and the patient was discharged home on day 12. The recommendation was given to re-initiate anticoagulation in non-valvular AF with 8000 IU of enoxaparin daily divided into two doses for 2 more weeks and thereafter warfarin based OAC should be restarted.

Discussion and Conclusions

Elderly patients are at known increased risk of bleeding associated with NOACs.⁸ It is unclear whether recommended dose reductions are sufficient in the very elderly. Therefore, vigilant monitoring is recommended, in particular during periods of acute illness

and following the introduction of potentially nephrotoxic drugs. In elderly patients with renal failure and polypharmacy, NOACs may therefore induce an incalculable effect on the coagulation system, which is difficult to monitor. In the case study presented here, following observation of major chest and abdominal wall bleeding, the primary suspect was of anticoagulation-related hemorrhage following recent initiation of RXN therapy. The body mass index of the patient of 29 kg/m² was in the range of the mean body mass index of 28 kg/m² of patients included in the ROCKET-AF (*rivaroxaban once daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation*) trial, and also the age of 78 years was consistent with the mean patient age of 73 years in ROCKET-AF.⁶

The baseline GFR, available to the NOAC prescribing specialist from the patient's medical records was calculated according to the MDRD formula which may overestimate renal function, especially in elderly females.⁹ At admission the patient was in hemorrhagic shock with acute, oliguric renal failure; serum creatinine was 5.6 mg/dL suggesting that deterioration of renal function must have already initiated, therefore, may have contributed to suspected RXN accumulation with associated coagulopathy.

After successful stabilization of the patient's hemodynamics by volume resuscitation including transfusion of PRBC together with the return of urine production and renal function, it was expected that no RXN should have been in circulation after 36-48 h as the half-life of the NOAC is short.¹⁰ Yet, coagulopathy remained unchanged with activated partial thromboplastin time (aPTT) and PT values significantly prolonged. According to a recent toxicology report on 223 cases of acute RXN overdose, PT, INR or aPTT is elevated only in a minority of patients regardless of the reported ingestion.¹¹ Available coagulation testing may or may not be pathologic in RXN intoxication and may not reflect risk of bleeding.¹² As the patient's PT values were repeatedly prolonged to an unusually high extent, higher than expected for RXN treatment alone, a different type of coagulopathy was considered. The patient had been prescribed warfarin and reported to have stopped taking it several days before being switched to RXN, however, INR monitoring had not been repeated. For that reason in the clinical bleeding management, a 4-factor PCC in combination with intravenous vitamin K was given for anticoagulant reversal, following which aPTT, PT and INR quickly normalized.

The hypothesis was that the patient continued OAC with warfarin despite reporting cessation of administration. On that basis, the prescribing physician initiated anticoagula-

tion with RXN without repeating an INR test. Confirmation of this hypothesis comes not only from effective anticoagulant reversal with PCC on day 3 but also from results of retrospective determination of circulating RXN and warfarin levels on days 1, 3 and 4. At admission on day 0, RXN was still detectable in plasma at a low, sub-therapeutic concentration which confirms that she had taken the drug, and levels were negative on day 3 when PT was still highly prolonged and only reversed with PCC; RXN was also negative on day 4, whereas warfarin was detectable in plasma in the therapeutic range on all three occasions.

Two considerations merit discussion:

- First of all, NOAC prescribing was inappropriate. Although the treatment was specialist initiated, known impaired renal function was not controlled immediately before starting nor was the INR reassessed in the patient who has been orally anticoagulated with warfarin immediately prior to RXN therapy. There remains considerable uncertainty about appropriate prescribing and dosing of NOACs in the real-world setting. In a recent Australian survey, a total of 34% of the study population were prescribed a NOAC inappropriately, of which 40% would have been contraindicated because of severe renal impairment; interestingly, appropriateness of hospital-initiated prescription was no different of prescription in community-initiated patients.¹³ In the present case, NOAC prescription was hospital-initiated

and performed in a specialist out-patient setting.

- Secondly, although RXN levels were low already on day 1 and the patient probably had continued warfarin, PT remained significantly prolonged to >300 s until day 3, which may be related to the drug-drug interaction. In healthy adults neither RXN nor warfarin significantly affected maximum plasma concentrations of the other drug, however, pharmacodynamic interaction between RXN and warfarin was observed showing that during co-administration, maximum INR and PT values were higher than with RXN or warfarin monotherapy.¹⁴ It is clear that association of NOACs with other anticoagulant drugs increases the bleeding risk. Furthermore, NOACs may have an additional impact on the INR (especially the FXa inhibitors), influencing the measurement while on combined treatment. It is unclear if this case study demonstrates this hypothesis as PT remained prolonged to >300 s until day 3 prior OAC reversal when warfarin levels were still in the therapeutic range but RXN had been extensively eliminated.

In patients with warfarin-induced coagulopathy, immediate reconstitution of the clotting system can be achieved by infusion of the carboxylated clotting factors as PCC.¹⁵ Idarucizumab is an antidote against the direct FIIa inhibitor dabigatran and available for clinical use.¹⁶ however, for RXN and other NOACs with direct anti-FXa activity, no specific anti-

doters are currently available.¹⁷ For the management of major life-threatening bleeding FXa inhibiting NOACs, most authorities recommend the use of 4-factor PCC.⁷ A 4-factor PCC was administered in combination with intravenous vitamin K because of ongoing coagulopathy and bleeding, and a lack of clarity regarding the anticoagulant requiring reversal, *i.e.*, RXN or warfarin or both. In effect, both PT and aPTT were immediately corrected, removing the need for additional PRBC transfusions. Effective reversal of RXN-induced PT prolongation with 4-factor PCC has been reported,¹⁸ however, immediate normalization of clotting parameters is a typical characteristic of 4-factor PCC administration in warfarin-induced coagulopathy.¹⁹ This immediate response in PT and aPTT values following 4-factor PCC administration in the present case supports the assumption from retrospective therapeutic drug monitoring results that, in contrast to the patient's information given to the NOAC prescribing physician, OAC with warfarin had not been stopped but continued in an uncontrolled manner.

Learning objectives

NOACs have been extensively studied in clinical trials with favorable major bleeding complication outcomes as compared to OAC with VKA, however, in real world settings increased bleeding associated with NOACs has been observed in patients under-represented

Table 1. Results of blood tests.

Parameter (reference)	Time of blood sampling							
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 11
Urea, mg/dL (15-43)	–*	–	183	–	–	113	–	–
Creatinine, mg/dL (<1.1)	5.6	5.2	4.0	3.1	2.2	1.5	1.19	0.98
GFR, mL/min/1.73 m ² (>90)	–	7	9	13	20	32	43	55
Lactate, mmol/L (0.5-1.6)	6.7	1.6	–	–	–	–	–	–
Troponin T, ng/L (<14.0)	162	171	–	–	–	–	–	–
Hemoglobin, g/dL (12-16)	6.0	8.7	8.9	9.5	8.7	9.7	10.7	11.1
Thrombocytes, /nL (150-410)	368	163	166	160	177	180	194	217
PT INR, ratio (0.8-1.20)	>9	>9	1.16	2.57	1.15	1.05	–	–
PT, s (<12.6)	>320	>320	12.8	28.0	12.6	11.6	–	–
aPTT ratio, s (0.7-1.2)	4.55	3.10	–	–	–	0.87	–	–
Antithrombin, % (75-125)	–	96	–	–	–	–	–	–
D-dimer, ng/mL (<500)	–	441	–	–	–	–	–	–
AST, U/L (0-35)	26	–	32	–	–	22	–	–
ALT, U/L (0-35)	11	–	14	–	–	12	–	–
Bilirubin, mg/dL (0.1-1.4)	1.0	0.4	1.1	–	–	–	–	–
Gamma-GT, U/L (0-40)	16	–	10	–	–	16	–	–
Rivaroxaban level, ng/mL	18.8 ^o	–	<5.0 ^{#,§}	<5.0 [#]	–	–	–	–
Warfarin level, ng/mL [^]	3.4	–	3.4	2.4	–	–	–	–

*-, not measured; ^oliquid chromatography tandem-mass spectrometry assay, linear range 5-500 ng/mL; measured results of triplicate prepared samples were 18.781, 18.466 and 19.287 ng/mL; ^llower limit of quantification (LLOQ), 5.0 ng/mL; [§]a small peak was observed at ~0.4 ng/mL, which is below the LLOQ and un-reportable; [^]measured results are of triplicate prepared samples; therapeutic range, 1-10 ug/mL. GFR, glomerular filtration rate (according to the *modification of diet in renal disease formula*); PT INR, prothrombin time international normalized ratio; aPTT, activated partial thromboplastin time; AST, aspartate transaminase; ALT, alanine transaminase; GT, glutamyl transferase.

in clinical trials, in particular patients 75 years of age and older. Inappropriate NOAC prescription in borderline renal dysfunction may put patients at particular bleeding risks when polypharmacy and other risks of pharmacotherapy are more frequently encountered as in the elderly. Switching OAC from VKA to NOAC also requires judicious prescribing and dosing of NOAC. Regular monitoring of concomitant medications and renal function are highly recommended.

References

1. Garvey B. Easy bruising in women. *Can Fam Physician* 1984;30:1841-4.
2. Farage MA, Miller KW, Berardesca E, Maibach HI. Clinical implications of aging skin: cutaneous disorders in the elderly. *Am J Clin Dermatol* 2009;10:73-86.
3. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation* 2014;129:837-47.
4. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;146:857-67.
5. Hanon O, Assayag P, Belmin J, et al. Expert consensus of the French Society of Geriatrics and Gerontology and the French Society of Cardiology on the management of atrial fibrillation in elderly people. *Arch Cardiovasc Dis* 2013;106:303-23.
6. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365:883-91.
7. Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. *Europace* 2015;17:1467-507.
8. Ogbonna KC, Jeffery SM. Risk versus benefit of non-vitamin K dependent anticoagulants compared to warfarin for the management of atrial fibrillation in the elderly. *Drugs Aging* 2013;30:513-25.
9. Maccallum PK, Mathur R, Hull SA, et al. Patient safety and estimation of renal function in patients prescribed new oral anticoagulants for stroke prevention in atrial fibrillation: a cross-sectional study. *BMJ Open* 2013;3:e003343.
10. Kubitza D, Becka M, Roth A, Mueck W. The influence of age and gender on the pharmacokinetics and pharmacodynamics of rivaroxaban-an oral, direct Factor Xa inhibitor. *J Clin Pharmacol* 2013;53:249-55.
11. Spiller HA, Mowry JB, Aleguas A Jr, et al. An observational study of the factor Xa inhibitors rivaroxaban and apixaban as reported to eight poison centers. *Ann Emerg Med* 2016;67:189-95.
12. Lindhoff-Last E, Ansell J, Spiro T, Samama MM. Laboratory testing of rivaroxaban in routine clinical practice: when, how, and which assays. *Ann Med* 2013;45:423-9.
13. Pattullo CS, Barras M, Tai B, et al. New oral anticoagulants (NOACs) - appropriateness of prescribing in real-world setting. *Intern Med J* 2016 [Epub ahead of print].
14. Moore KT, Byra W, Vaidyanathan S, et al. Switching from rivaroxaban to warfarin: an open label pharmacodynamic study in healthy subjects. *Br J Clin Pharmacol* 2015;79:907-17.
15. Sarode R, Milling TJ Jr, Refaai MA, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. *Circulation* 2013;128:1234-43.
16. Pollack CV Jr, Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. *N Engl J Med* 2015;373:511-20.
17. Ansell JE. Reversing the effect of oral anticoagulant drugs: established and newer options. *Am J Cardiovasc Drugs* 2016 [Epub ahead of print].
18. Perzborn E, Heitmeier S, Laux V, Buchmüller A. Reversal of rivaroxaban-induced anticoagulation with prothrombin complex concentrate, activated prothrombin complex concentrate and recombinant activated factor VII in vitro. *Thromb Res* 2014;133:671-81.
19. Goldstein JN, Refaai MA, Milling TJ Jr, et al. Four-factor prothrombin complex concentrate versus plasma for rapid vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions: a phase 3b, open-label, non-inferiority, randomised trial. *Lancet* 2015;385:2077-87.