Correlation between rivaroxaban (Xarelto) plasma activity, patient clinical variables and outcomes in a South African centre

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Background. Low-molecular-weight heparin and vitamin K antagonists such as warfarin are the gold standard for prohylaxis and treatment of venous thromboembolic disease (VTED). Direct oral anticoagulants (DOACs) result in predictable anticoagulation with significantly reduced inter- and intra-patient variability. DOAC absorption is rapid, with a short half-life and relatively few drug interactions. DOACs are effective and safe at fixed doses without activity monitoring. However, specific situations may require assessment of accurate drug activity. Rivaroxaban, a DOAC targeting activated coagulation factor X (FXa), is registered for the prevention and treatment of VTED in South Africa.
Objectives. To establish a prophylactic rivaroxaban activity level range and determine any associations with clinical complications, viz. haemorrhage and/or thrombosis.
Methods. Samples from 115 orthopaedic patients were tested 3 hours after a prophylactic oral dose of 10 mg rivaroxaban with STAGO rivaroxaban anti-FXa reagent on an automated coagulation analyser. Patient demographics and clinical outcomes were documented.
Results. The mean rivaroxaban anti-FXa level was 105.7 ng/mL. Two patients developed adverse events on therapy. One patient had minor bleeding (menorrhagia) (drug activity level 288.7 ng/mL) and another a deep-vein thrombosis (drug activity level 34.7 ng/mL). Statistical analysis demonstrated an association between drug activity and advancing age (p=0.008), most apparent among those aged ≥65 years.
Conclusions. Measuring rivaroxaban activity levels may reduce uncertainty if treatment failure and complications occur. Patients aged ≥65 years should be closely monitored. A local expected rivaroxaban activity level for patients on rivaroxaban prophylaxis has been established.

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Heparin and warfarin, a vitamin K antagonist, were first widely used to treat venous thromboembolic disease (VTED) in the early 1940s.[1] Later low-molecular-weight heparin followed by a vitamin K antagonist became the recommended therapeutic regimen.[2] Vitamin K antagonists have also been the drugs of choice in preventing thromboembolic events in patients with atrial fibrillation. The major problem with warfarin has been unpredictable pharmacodynamic and pharmacokinetic properties, including food and drug interactions, with resultant marked fluctuation in anticoagulation control in a significant number of patients. This, together with the large number of patients on long-term oral anticoagulation, has been the impetus for the development of oral alternatives by pharmaceutical companies.[3,4]

Direct oral anticoagulants (DOACs) target individual activated coagulation factors, and their pharmacological properties are detailed in Table 1. These agents have been investigated in multicentre trials to establish efficacy and safety in the treatment and prevention of venous thromboembolism in many clinical conditions (Tables 2 and 3). The two agents registered in South Africa (SA) to date are rivaroxaban (Xarelto; Bayer), a direct factor Xa (FXa) inhibitor, and dabigatran (Pradaxa; Boehringer Ingelheim), a factor IIa (thrombin) inhibitor. Both these agents are currently registered in SA for the treatment and prevention of VTED, i.e. deep-vein thrombosis (DVT) and pulmonary embolism (PE), as well as for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

Because up to 80% of the active component of dabigatran is excreted renally, any renal impairment, especially in the elderly, can result in toxicity with resultant haemorrhage. Although the rate and severity of major haemorrhage were lower in trial patients on rivaroxaban than in those on standard therapy, overall haemorrhagic complications occurred with the same frequency.[4]

Studies have demonstrated DOACs to be effective and safe at fixed doses without laboratory activity monitoring. Evidence has shown that qualitative drug activity information seems to be adequate in most clinical situations. There are, however, specific situations where assessment of accurate drug activity levels may be required (Table 4).[5,6]

The lack of requirement for routine monitoring of DOACs is based on the assumed similarity in pharmacokinetic and pharmacodynamic responses between individuals with varying demographics, including age, race, gender, renal function and body mass index (BMI). It has, however, been estimated that the same dose of a DOAC can produce an up to 30% difference in thrombin generation inhibition.[7] There has been speculation that bleeding would be more likely in high responders and thrombosis more likely in low responders. Clinical trials usually exclude patients with impaired renal function, extremes of age (i.e. <18 and >65 years), those with an increased bleeding risk and those at the extremes of body weight. The lack of a need to monitor that was demonstrated in the trials may therefore not be applicable in real-life situations.

Table 1. Overview of DOACs registered in SA[3]

	Rivaroxaban	Dabigatran
Mechanism of action	Direct FXa inhibitor	Direct thrombin inhibitor
Route of administration	Oral	Oral (prodrug)
Fixed-dose administration	Yes	Yes
Onset of action	Rapid (within 2 hours)	Rapid (within 2 hours)
Pharmacokinetics: bioavailability after oral administration	60 - 86%	~6%
Half-life	7 - 11 hours	14 - 17 hours
Excretion	Biliary/faecal (28%); renal (33% metabolised, 33% excreted unchanged)	Renal (80%)
Anticoagulant response	Predictable	Predictable
Routine coagulation monitoring needed	No	No
Food interactions	Absorption moderately increased by food	Delayed absorption with food
Drug interactions	Ketoconazole, itraconazole, voriconazole, posaconazole, fluconazole, ritonavir, phenytoin, carbamazepine, phenobarbital, aspirin, NSAIDs, St John's wort, rifampicin	NSAIDs, St John's wort, rifampicin, verapamil, clarithromycin, amiodarone, verapamil, aspirin (with higher doses of dabigatran)
Risk of thrombocytopenia	Minimal	Minimal

NSAIDs = non-steroidal anti-inflammatory drugs.

Table 2. High-level summary rivaroxaban clinical trials

Clinical indication	Trial name, year, *n*	Treatments	Trial design, number of participating countries
VTED prophylaxis in total hip and knee arthroplasty	RECORD 1-3, 2008, *n*=4 772 v. 4 809	Rivaroxaban 10 mg orally v. enoxaparin 40 mg subcutaneously once daily	Parallel groups, double blind, 27 countries
VTED treatment: DVT and PE	Einstein-DVT and PE, 2010/ 2012, *n*=4 150 v. 4 131	Rivaroxaban 15 mg twice daily for 3 weeks, then 20 mg daily v. standard therapy (enoxaparin followed by warfarin)	Parallel groups, open label, 38 countries
SPAF	ROCKET-AF, 2010, *n*=7 131 v. 7 133	Rivaroxaban 20 mg daily v. warfarin	Parallel groups, double blind, 45 countries

n = number of patients on study drug v. number of patients on standard therapy; SPAF: stroke prevention in atrial fibrillation.

Table 3. High-level summary dabigatran clinical trials

Clinical indication	Trial name, year, *n*	Treatments	Trial design, number of participating countries
VTED prophylaxis in total hip arthroplasty	RE-NOVATE, 2007, *n*=2 184 v. 2 165	Dabigatran 150 or 220 mg/d v. enoxaparin 40 mg/d	Parallel groups, double blind, multiple countries
VTED treatment: DVT and PE	RE-COVER, 2009/2011, *n*=2 568 v. 2 560	Dabigatran 150 mg twice daily v. warfarin	Parallel groups, double blind, 31 countries
SPAF	RE-LY, 2010, *n*=12 257 v. 12 114	Dabigatran 110 or 150 mg daily v. warfarin	Parallel groups, open with blinded assessment, 44 countries

n = number of patients on study drug v. number of patients on standard therapy; SPAF = stroke prevention in atrial fibrillation.

A study by Reilly *et al.*[8] on the effect of dabigatran plasma concentrations showed that laboratory measurement of drug activity is important and suggests that testing will become more widespread in the future as doctors strive to reduce complications and improve efficacy. This study concluded that both ischaemic stroke and bleeding outcomes correlated with dabigatran plasma concentrations. It is therefore important for clinical laboratories to have the ability to measure drug activity rapidly.

Rivaroxaban exerts a direct anti-FXa activity in plasma. The rational choice to measure direct FXa-inhibitors is therefore an anti-FXa assay. A number of studies have concluded that anti-FXa chromogenic assays are more specific and sensitive than routine clotting test-based assays. In addition, there is a better correlation between plasma concentrations measured by liquid chromatography/mass spectrometry and levels estimated by anti-FXa assays than those obtained using the routine prothrombin time (PT) assay. The rivaroxaban anti-FXa assay demonstrates an adequate linearity response to increasing concentrations of rivaroxaban.[9,10] Commercial reagents are available for measuring rivaroxaban anti-FXa activity on routine automated coagulation analysers. It is essential for every laboratory to establish its own reference range in its patient-specific population and laboratory environment.[5,8]

Objectives

To establish an expected rivaroxaban activity level for patients on prophylactic doses of

Table 4. Clinical situations in which the measurement of DOAC anticoagulant activity is potentially useful

When stable anticoagulation is achieved (1 - 2 weeks after initiation)
Before surgical or other invasive procedures
Adverse events (haemorrhage or thrombosis)
Before and after introducing additional drugs which are known to interact
Extremes of body mass index
Suspected overdose
When bridging from one anticoagulant to another
To assess compliance
To exclude drug accumulation in the elderly
To assess pharmacological activity, i.e. quality control
In patients with renal or hepatic dysfunction

Table 5. Demographic and clinical characteristics of the patients (*N*=115)

Factor	*n* (%)
Gender	
Male	59 (51.3)
Female	56 (48.7)
Age (yr)	
<65	89 (77.4)
≥65	26 (22.6)
BMI	
Underweight	1 (0.9)
Normal	15 (13.0)
Overweight	43 (37.4)
Obese	56 (48.7)
eGFR (mL/min)	
<60	9 (7.8)
≥60	106 (92.2)
Anti-FXa (ng/mL), mean (SD)	105.7 (58.61)

Table 6. Associations between demographic and clinical characteristics and anti-FXa levels

Factor	Anti-FXa (ng/mL), mean (SD)	*p*-value
Gender		
Male	100.54 (51.35)	
Female	111.83 (65.32)	0.283
Age group (yr)		
<65	98.09 (55.09)	
≥65	132.14 (63.61)	0.009
BMI		
Normal	83.54 (50.01)	
Overweight	118.72 (59.80)	
Obese	100.62 (58.12)	0.095
eGFR (mL/min)		
<60	136.64 (52.14)	
≥60	103.17 (58.60)	0.100

rivaroxaban as well as to assess any association between clinical complications, viz. haemorrhage and/or thrombosis, and drug levels.

Methods

This was a cross-sectional pilot study measuring rivaroxaban anti-FXa activity in orthopaedic patients admitted to a private hospital in Gauteng Province, SA, for elective foot and ankle surgery. The study was conducted over a 9-month period between 2014 and 2015. Ethics approval was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg, and unconditional approval was given (ref. no. M131165).

Venous blood was collected from 115 consecutive orthopaedic patients post surgery, 3 hours after administration of a prophylactic oral dose of 10 mg rivaroxaban. Patient demographics (age, race, gender, BMI and estimated glomerular filtration rate (eGFR)) as well as clinical outcomes were documented. Blood samples were analysed with STAGO rivaroxaban anti-FXa reagent on an automated coagulation analyser after successful calibration and performance of controls. Drug activity was measured as anti-FXa activity in ng/mL.

Statistical analysis

A descriptive analysis was conducted which included summary measures, i.e. mean and standard deviation (SD) for continuous variables such as age, BMI and eGFR. We also presented the mean (SD) for anti-FXa as an outcome variable. Frequency tabulations were also presented for categorical variables: gender, age group (<65 years and ≥65 years) and BMI (categorised into underweight, normal, overweight and obese).

An investigation of statistical associations between the outcome variable and demographic factors was performed using a *t*-test for comparing two groups and analysis of variance (ANOVA) where more than two groups were being compared. The tests were conducted at a 5% significance level. Further, a linear regression analysis was conducted through a univariate regression model. Factors found significant at a 20% level in the univariate analysis were then considered in the multiple linear regression analysis.

Results

A total of 115 patients, of whom 56 (48.7%) were female, were included (Table 5). The mean age was 54 years (SD 15), with 89 patients (77.4%) being <65 years of age. Ninety-nine patients (86.1%) were overweight (BMI >25), with 56 (56.6%) classified as obese.

The mean rivaroxaban anti-FXa level in the study population 3 hours after receiving a 10 mg dose was 105.7 ng/mL (95% confidence interval (CI) 94.9 - 116.6).

Two patients experienced adverse events on rivaroxaban therapy. A 43-year-old woman with normal renal function and an elevated BMI of 40 had minor bleeding (menorrhagia) without a decrease in haemoglobin. Her rivaroxaban level was 288.7 ng/mL. The second adverse event occurred in a 47-year-old man who developed a below-knee DVT. He had a normal BMI of 22, with a rivaroxaban activity level of 34.7 ng/mL.

After considering significant factors at univariate level, the final multiple linear regression model demonstrated a statistically significant association between drug activity and advancing age (p=0.008), this being most apparent among patients aged ≥65 years. Creatinine clearance as estimated by the eGFR, however, did not demonstrate a statistically significant association with drug level (p=0.100). There was no association between drug level and the other demographic variables, such as gender (p=0.283) and BMI (p=0.095) (Table 6).

Conclusions

Commercial assays are available to measure rivaroxaban anti-FXa activity. The clinical application of rivaroxaban activity levels may reduce uncertainty in the event of treatment failure and bleeding complications. The mean rivaroxaban anti-FXa level in the study population 3 hours after receiving

a 10 mg dose was 105.7 ng/mL, with a range of 25.0 - 283.2. This preliminary pilot study demonstrated a statistically significant association between advanced age and rivaroxaban activity levels, but no association with eGFR. Estimated creatinine clearance reflected by the eGFR is, however, not sensitive enough to detect deterioration in renal function, especially with advancing age.[11] Not only are elderly patients at an increased risk of venous thromboembolism, but they are also at an increased risk of bleeding. Increase bleeding risk in the elderly is related to comorbid diseases such as hypertension and malignancy, deteriorating renal function, polypharmacy and frailty with an increased risk of falls.[12,13] Although the significance of the increased rivaroxaban activity levels in the elderly is unknown, this study suggests that patients aged ≥65 years on therapy should be closely monitored. A local expected rivaroxaban activity level for patients on prophylactic therapy has been established.

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