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Direct oral anticoagulant drug level testing in clinical practice: a single institution experience

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Abstract

We performed a review of all direct oral anticoagulant (DOAC) levels – ecarin times for dabigatran and anti-Xa levels for rivaroxaban and apixaban – ordered at our institution with the purpose of evaluating DOAC levels from “real-world” (non-clinical trial) patients taking DOACs long-term, in order to assess levels obtained, reasons for checking levels, and actions taken based on the testing result. A total of 28 patients had 48 levels sent over a 36-month period. The majority of outpatient levels were within or close to the range of published values. The setting in which levels were sent influenced how results affected management decisions: in the outpatient setting, the majority of levels served to reassure clinicians that DOAC levels were within expected ranges resulting in continuation of chosen management, whereas in the inpatient setting, DOAC levels were used most frequently to detect DOAC presence in urgent clinical situations and influenced clinical decision-making in the peri-procedural and pre-operative periods. Our results demonstrate that while testing may be useful if immediately available in urgent clinical situations where assessment of drug presence is needed, DOAC level monitoring is infrequently used overall, and the lack of use combined with the paucity of available evidence to guide clinical decision-making based on the results suggests there is little urgency to make the tests widely available for routine use outside of acute settings in the emergency department and urgent surgical setting.

Keywords

direct oral anticoagulant (DOAC); monitoring of anticoagulation

Introduction/ Background

Four direct oral anticoagulants (DOAC) are currently approved in the United States and other countries for the treatment of venous thromboembolic disease and for stroke prevention in atrial fibrillation: the thrombin inhibitor dabigatran, and the factor Xa inhibitors apixaban, rivaroxaban, and edoxaban. DOACs are given at fixed doses and are

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marketed for use without the need for routine monitoring. However, there are instances in which measurement of anticoagulant activity may be desirable, such as prior to surgery to detect residual anticoagulant drug effect, in the setting of bleeding complications or occurrence of thrombosis while on anticoagulant therapy, in the case of suspected non-compliance, and in special patient populations such as extremes of body weight and renal impairment.

Assays for measuring the effects of anti-Xa drugs (via anti-Xa levels) and dabigatran (ecarin clot time, dilute thrombin time [dTT]) have been validated for clinical testing, though they are not yet FDA approved or widely available. However, interpretation of the DOAC levels is difficult. Most published information of DOAC levels at particular doses comes from plasma levels obtained from small studies of healthy volunteers or pharmacokinetic modeling from phase II and III studies,[1-10] making the applicability to actual patients taking the drugs chronically questionable. Data on levels from non-clinical trial patients is limited to a small number of case series with small to moderate numbers of patients.[11-14]

Furthermore, while “expected ranges” or “on- therapy ranges” of drug levels have been published, therapeutic ranges of dabigatran levels and anti-Xa anticoagulant levels have not been defined. While two studies found an association between drug levels and clinical outcomes-namely, that the risk of major bleeding is increased as plasma levels of edoxaban and dabigatran increase, and the risk of ischemic stroke and systemic thromboembolism is associated with lower drug levels [6,15] - no studies have correlated clinical outcomes with specific drug levels. Thus, clinical decisions, such as dose-adjustments based on drug levels, are problematic and no evidence exists for the effectiveness of such practice. And, indeed, while clinical practice statements recognize that these levels can be used to detect drug presence or to quantify drug levels, they give no further guidance on how to interpret results or adjust drug dosing based on levels.[16,17]

In this manuscript, we review the DOAC levels ordered at our institution, in order to publish actual plasma levels from patients taking the drugs long-term in comparison to published expected levels, to review the indications for DOAC level testing, and to review management decisions based on the results.

Methods

This study was approved by the Institutional Review Board of the University of North Carolina. Through query of our clinical laboratories, we identified patients who had rivaroxaban anti-Xa testing, apixaban anti-Xa testing, or dabigatran ecarin time (ECT) ordered at our institution from June 2012 through July 2015 (edoxaban levels were not available for clinical testing at our institution during this time). We then performed a retrospective chart review to collect data, including demographic information, laboratory data, and clinical information such as indication for anticoagulation, medication dosage, and reason for sending a drug level. Data was extracted from the medical records by one reviewer (KM).

At our institution, apixaban anti-Xa and rivaroxaban anti-Xa levels are sent out to a collaborating laboratory, and while anti-Xa levels are ordered, the test is actually run by liquid chromatography- mass spectrometry (LC-MS) and reported as anti-Xa drug level by the collaborating laboratory. Dabigatran ecarin times are performed in-house.

Results

Patient population

A total of 28 patients had 48 DOAC levels sent at our institution over the specified time period (Table 1). Nearly half (57%) of patients were female, and the age of patients ranged from 21 to 88 years, with a median age of 47 years. Body mass index (BMI) ranged from 14.9 kg/m^2 to 66.8 kg/m^2, with a median BMI of 31.3 kg/m^2, and weight ranged from 44.5 kg to 203.9 kg, with a median of 101.9 kg. Most patients (86%) had an estimated glomerular filtration (eGFR) of greater than 60 mL/min/1.73m^2, with the exception of one patient with an eGFR of 11 mL/min/1.73m^2 and three patients with eGFRs ranging from 30-60 mL/min/1.73m^2.

Drug levels

A total of 48 levels have been sent for testing over the specified time period, June 2012 through the first half of 2015. While no levels were sent in 2012 and only two levels were sent in 2013, the number of levels sent for testing significantly increased to 29 in 2014 with the availability of apixaban and rivaroxaban testing. Through the first half of 2015, the numbers of levels sent for testing remained approximately the same as in 2014, totaling 17.

Eight patients had a total of nine apixaban levels sent, including one patient who had a peak and trough pair. Fifteen patients had 24 rivaroxaban levels sent, including four patients with peak and trough pairs, and five patients had 15 dabigatran levels sent. Apixaban anti-Xa levels ranged from 93.3 to 274 ng/mL. Six of eight patients taking apixaban were dosed at 5 mg twice daily, and for those patients, peak apixaban anti-Xa levels ranged from 110.6 to 240.3 ng/mL, with mean peak level of 184.9 ng/mL. Rivaroxaban anti-Xa levels ranged from 0 to 459.8 ng/mL. Fourteen of fifteen patients in the rivaroxaban cohort were taking a dose of 20 mg daily; for these patients peak values ranged from 123.7 to 459.8 ng/mL, with a mean peak of 202.0 ng/mL. There were four trough rivaroxaban anti-Xa levels for subjects on 20 mg daily, with values ranging from 0 to 37.8 ng/mL, with a mean trough of 17.6 ng/mL. As noted above, most dabigatran levels were checked in the pre-operative or pre-procedural setting with intent of monitoring until low levels were obtained, rather than for range estimates. Ten obese patients with a BMI >40 kg/m^2 had DOAC levels sent, including three on apixaban and seven on rivaroxaban, and two of these patients had a trough level measured at 0 ng/mL.

Testing indications

Sixteen levels from six patients were sent when the patients were inpatient and 32 levels sent on 22 outpatients. The majority of dabigatran levels (13 levels in 3 patients) were checked pre-operatively or pre-procedurally. Extremes of body weight represented the most common reason for checking DOAC levels, with 15 levels checked in nine obese patients, and five

levels checked in two patients with low body weight. Other indications for checking anti-Xa levels included concern for drug failure (five patients, five levels), post-gastrointestinal surgery (two patients, two levels), and concern for medication interaction (one patient, two levels).

Clinical consequences of test results

Of the levels checked in the outpatient setting, the results had several consequences. In 82% (9/11) of patients with extreme body weights and one patient post-gastric bypass (Table 1, patient 21), levels fell within published ranges, leading to clinician's comfort in continuing the chosen management. Levels fell below the expected ranges in two patients with obesity and one patient post-bowel resection (Table 1, patient 22), but no action was taken based on results for unclear reasons. In one patient on an antifungal medication (Table 1, patient 20), the DOAC level did not significantly change after starting the antifungal medication, leading to comfort in continuing both medications concurrently. In the 5 patients for whom testing was sent because of new thrombotic symptoms, one was determined to have “failed” DOAC and was switched to low molecular weight heparin (LMWH) in the setting of malignancy (Table 1, patient 7), another was determined not to have an indication for anticoagulation and was started on aspirin (Table 1, patient 4), and the remaining three were ultimately determined not to have recurrent thrombosis and were maintained on the same dose when levels were within expected ranges.

Of levels checked in the inpatient setting to detect drug presence, DOAC results influenced management decisions: the presence of dabigatran as determined by ECT delayed surgery and procedures for two patients, including central line placement and renal biopsy, as the bleeding risk was thought to be too high given the level of dabigatran. For another patient, the dabigatran level drawn pre-operatively was undetectable, and she, therefore, underwent the scheduled surgery.

Discussion

Our case series adds to the growing body of data of DOAC levels in actual patients taking the drugs long-term, supplementing the available literature of published DOAC levels that have been obtained mostly from healthy volunteer studies or from PK/PD modeling of large clinical trials.[11-14, 18]

Our data show that the rivaroxaban levels in our patients are generally comparable to published levels, though the lowest peak and trough levels in our study were lower than the low ends of most published data. This particularly holds true for the obese patients in our cohort taking rivaroxaban, for which two out of five trough levels were 0, suggesting possible under-dosing of rivaroxaban in these patients. Published apixaban drug level data are less plentiful than for rivaroxaban and lack ranges of mean values, though our median peak as well as two trough levels of apixaban are higher than the means published for 5 mg twice daily dose.[2, 19] As described above, the majority of dabigatran levels at our institution were drawn in order to detect presence of drug prior to proceeding with procedures and/or operations, but the two values that were checked as outpatients are consistent with published ranges.[6, 12] Our data also confirms the wide inter-patient

variability that has been described previously in a small number of studies.[12-14, 18] The retrospective nature of our study depended on the chart documentation of the times the drugs were taken by the patient and, therefore, the peak and trough timing of levels may not be precise; however, this is representative of "real-world" management of anticoagulation in clinical practice.

We found the reasons that DOAC levels were checked consistent with published proposals on why levels might be checked;[17] the most common reason for testing in our cohort was extreme of body weight- mostly obesity, but also low body weight. Other indications for checking levels included recurrent thrombosis, past bowel resections with concerns for drug suboptimal absorption, and medication interactions. In our study, the setting and reasons for testing influenced actions taken based upon the result: levels checked in the outpatient setting were used to reassure clinicians that DOAC levels were within expected ranges, leading to comfort in continuing present management, while in the inpatient setting, clinical decisions and management were influenced by DOAC testing with timing of surgery/ procedures affected by dabigatran level results.

While there has been interest in the general medical community in making drug levels more widely and readily available, our experience suggests testing is uncommonly used and rarely affects routine decision-making, and, therefore, may not be urgently needed. We estimate that approximately 500 patients are on DOACs and followed regularly by a provider at our institution at any given time, and despite this high-volume, DOAC testing has been infrequently used since testing has been available (one year for rivaroxaban and apixaban anti-Xa levels and three years for dabigatran ECT). We acknowledge that the volume of testing may be influenced by both lack of provider awareness of the existence of such tests as well as slow turn-around time (currently samples for apixaban and rivaroxban level testing are sent out to collaborating labs and typical results return in approximately ten days), although we would not expect the long turn-around time to significantly influence decisions to send tests on more routine monitoring in the outpatient setting. In addition to infrequent use of DOAC level testing, data is lacking on how to make clinical decisions based on these levels: for only two studies have correlations between plasma drug levels and clinical outcomes in patients with atrial fibrillation been published, demonstrating that the risk for thrombosis increases as plasma levels of dabigatran decrease,[6] and the risk for major bleeding increases with higher dabigatran and edoxaban levels.[6, 15] Correlations between specific drug levels and clinical outcomes (thrombosis or bleeding), however, have not been established. Interpretation of results is also hampered by the fact that for at least one DOAC, dabigatran, there is significant intra-individual drug level variation when testing the same patient at different times [18]; there have not been studies to date about intra-patient variability in the anti-Xa inhibitors.

As seen by our data – preoperative dabigatran plasma levels to determine best time for an urgent surgery and procedures – and as proposed by other authors, DOAC level testing may be useful in urgent and emergent situations in which assessment of drug presence is needed, such as trauma, stroke, hemorrhage, or need for emergent surgery or procedures.[20-23] These situations represent instances in which assays with drug-specific calibrations would be helpful to allow for rapid assessment of DOAC levels. The value of such tests, however,

depend on their turn-around time, and as such, would need to be performed in-house. In the absence of widespread availability of DOAC–specific calibration, alternatives such as anti-Xa assays with low-molecular weight heparin calibration may be useful in excluding significant anti-Xa drug levels,[20, 24, 25] which may make immediate availability of drug-specific anti-Xa assays less critical.

In conclusion, our results demonstrate plasma levels attained from actual patients taking the drugs long-term to supplement published data from volunteers and clinical trials. We found that DOAC drug level testing is uncommonly used in routine clinical practice at our institution that sees a high-volume of patients anticoagulated with DOACs. While immediate availability of drug level assessment is likely beneficial in situations where urgent assessment of drug presence is needed, such as trauma, stroke, hemorrhage, or need for emergent surgery or procedures, our data suggest that there is otherwise little urgency to make the DOAC testing widely available for routine clinical practice. Moreover, interpretation and clinical management using DOAC-level results becomes challenging in light of the absence of data to guide management in dosing based on these levels. Further work is needed to establish correlation between specific drug levels and clinical outcomes in order to determine appropriate indications for testing and to maximize the utility of DOAC testing.

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Highlights

- DOAC testing results from patients taking anticoagulation long-term are presented
- Reasons for testing and clinical consequences of DOAC level results are explored
- DOAC level testing is infrequently used at our institution

Table 1

Patient demographics, reason for sending DOAC level, and results of DOAC testing

Patient	Reason for testing	Age (years)	Gender M=male, F= female	BMI (kg/m^2)	Weight (kg)	Dose (QD= daily, BID=twice daily)	DOAC level (ng/ml)*	Peak vs trough	Miscellaneous Notes	Outcome
Apixaban										
1	obesity	64	F	50.7	139.8	5 mg BID	240.3	peak		no change
2	obesity	41	F	66.8	199.1	5 mg BID	110.6	peak		no change
3	low body weight	88	F	22.6	54.3	2.5 mg BID	102 218.5	trough peak		no change
4	recurrent TTP with stroke on apixaban	45	F	34.5	82.8	5 mg BID	229.5	peak	inpatient	stopped apixaban, resumed aspirin
5	Livedoid vasculopathy with persistent symptoms in spite of a/c	66	M	28.1	90.2	5 mg BID	93.3	random	8 hour post dose	no change
6	healing leg ulcer with palpable clotted veins around it	28	M	27.3	86.2	5 mg BID	159	peak	4 hours post dose	no acute thrombus, no change to dose
7	progressive superior mesenteric vein thrombosis in spite of apixaban	62	F	46.2	-	7.5 mg BID	274	peak	inpatient; 4 hour post dose	switched to LMWH in setting of malignancy
8	unclear	70	F	27.4	70.2	5 mg BID	269.2	trough		no change
Rivaroxaban										
9	obesity	27	M	56.2	203.9	15 mg BID	0	trough	17 hours post-dose	no change
10	obesity	40	M	43.6	-	20 mg QD	222.3	peak	3 hours post-dose	no change
11	obesity	47	M	40.7	150	20 mg QD	15.5	trough		no change

Patient	Reason for testing	Age (years)	Gender M=male, F= female	BMI (kg/m^2)	Weight (kg)	Dose (QD= daily, BID=twice daily)	DOAC level (ng/ml) *	Peak vs trough	Miscellaneous Notes	Outcome
							205.6	peak	2.5 hours post-dose	
12	obesity	33	F	51.2	148.3	20 mg QD	96.5	random		no change
							37.8	trough		
							459.8	peak		
13	obesity	43	M	44.9	158.8	20 mg QD	142.4	peak		no change
							17	trough		
							134	random		no change
14	obesity	47	F	59.3	161.6	20 mg QD	139.1	random	no documentation	no change
15	obesity	47	F	50.1	140.6	20 mg QD	0	trough	24 hours	no change
							123.7	peak	2.5 hours post-dose	
16	low body weight	30	F	20	44.5	15 mg QD	155.5	peak		no change
							5.8	peak		no change
							116	peak		no change
17	concern for new thrombus, rule out anticoagulation failure	38	M	26.6	96.5	15 mg BID	161.6	peak		determined thrombus developed prior to rivaroxaban inittiation; thus no change
18	history of supratherapeutic INR on warfarin, concern for overdosing of rivaroxaban	29	F	22.8	60.1	20 mg QD	19.4	random		no change
19	history of bleeding at lower dose	54	F	NR	NR	20 mg QD	282.6	peak	3 hours post-dose	no change
20	starting terbinafine-concern for	53	M	31.6	103.4	20 mg QD	250.3	peak		no change

Patient	Reason for testing	Age (years)	Gender M=male, F= female	BMI (kg/m^2)	Weight (kg)	Dose (QD= daily, BID=twice daily)	DOAC level (ng/ml) *	Peak vs trough	Miscellaneous Notes	Outcome
	medication interaction									
	post-terbinafine dose						210.1	peak	level checked one week after starting terbinafine	no change
21	post gastric bypass	60	F	30.9	100.4	20 mg QD	125.8	peak	4 hours post-dose	no change
22	s/p bowel resection	21	M	30.9	106.2	20 mg QD	0	random		no change
23	unclear	70	M	27.6	87.3	20 mg QD	194	peak	4 hours after last dose	no change
Dabigatran										
24	acute on chronic renal failure, need for line placement	59	M	37.6	NR	150 mg QD	194	random	7d after last dose	monitored level until renal biopsy performed without complication
							155	random	8d post-dose	
							128	random	9d post-dose	
							117	random	10d post-dose	
							88	random	11d post-dose	
							66	random	12d post-dose	
							66	random	13d post-dose	
							44	random	15d post-dose	
							54	random	16.5d post-dose	
25	need for urgent surgical intervention	75	M	25.2	NR	NR	91.72	random	24 hours post-dose	levels monitored in preparation for surgery; ultimately never underwent surgery
							65	random	48 hours post-dose	
							46.1	random	7d post-dose	

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Patient	Reason for testing	Age (years)	Gender M=male, F= female	BMI (kg/m^2)	Weight (kg)	Dose (QD= daily, BID=twice daily)	DOAC level (ng/ml) *	Peak vs trough	Miscellaneous Notes	Outcome
26	pre-op	65	F	14.9	81.6	150 mg BID	<30	random	24 hours post-dose	repair of wound dehiscience of deep brain stimulator
27	APLAS	21	F	21.9	NR	150 mg BID	85.11	peak	1 hour post-dose	no change
28	prolonged PT/PTT	59	F	NR	108	150 mg BID	92	random		dabigatran held in setting of prolonged PTT/PT due to liver synthetic dysfunction

* Determined by liquid chromatography- mass spectrometry (LC-MS) and reported as anti-Xa drug level for apixaban and rivaroxaban and by chromogenic ecarin assay for dabigatran

Abbreviations: BMI= body mass index; INR= international normalized ratio; APLAS = anti-phospholipid antibody syndrome; PT= prothrombin time; PTT= partial thromboplastin time; d=days, hrs= hours

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