Clinical Feasibility of Monitoring Enoxaparin Anti-Xa Concentrations: Are We Getting It Right?

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ABSTRACT

Background: Anti-Xa monitoring is utilized to measure the extent of anticoagulation in certain patient populations receiving enoxaparin. It is essential to accurately obtain this pharmacodynamic marker for safe and effective anticoagulation management.

Objectives: To determine the frequency of correctly drawn anti-Xa concentrations in accordance with predefined institutional criteria and to determine the number of dose adjustments implemented based on incorrectly drawn anti-Xa concentrations.

Methods: This was a retrospective, single-center, cohort study among adult patients who received treatment doses of enoxaparin with measured anti-Xa concentrations. Patients were excluded if they were pregnant, on hemodialysis, or received prophylactic dosing. Anti-Xa levels were defined as correctly measured if they were drawn 3 to 5 hours after the dose during steady state concentrations. Descriptive statistics were performed and analyzed via SPSS software.

Results: Overall, 203 patients were reviewed and 59 patients with 74 anti-Xa levels were included. The majority of anti-Xa levels (57/74; 77%) were drawn incorrectly and often resulted in collection of repeat anti-Xa samples. There were 12 documented dose adjustments and approximately 42% (5/12) were based on incorrectly drawn anti-Xa levels. Anti-Xa levels were within target range approximately 45% of the time.

Conclusions: Enoxaparin anti-Xa concentrations are frequently drawn incorrectly and dose adjustments are often performed based on these unsupported anti-Xa levels. This may present a potential risk to compromise patient safety.

Key Words—anti-Xa monitoring, enoxaparin, low molecular weight heparin, pharmacodynamic monitoring

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Low molecular weight heparin (LMWH), including enoxaparin, is a routinely utilized anticoagulant among hospitalized patients for various indications.¹⁻³ Because it is not possible to measure LMWH concentrations directly, surrogate pharmacodynamic markers, such as anti-Xa concentrations,

can be measured to determine the extent of anticoagulation in patients receiving enoxaparin.⁴⁻⁶

Enoxaparin demonstrates predictable pharmacokinetics and pharmacodynamics in the majority of clinically stable adults, thus routine anti-Xa monitoring for anticoagulation effects is typically not

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recommended.^{2,4,7-10} For certain patient populations, however, anti-Xa monitoring may be warranted to ensure safe and effective anticoagulation where optimal dosing is less predictable. These patient characteristics include renal or hepatic insufficiency, extremes of body weight (≤ 40 kg or ≥ 150 kg), newborns, children, pregnancy, prolonged therapy (≥ 7 -10 days), and advanced age.^{8,11-17} Furthermore, there are not strong data to support the use of anti-Xa monitoring in the majority of patients receiving enoxaparin outside of these select patient populations. Enoxaparin anti-Xa monitoring may be difficult and often incorrect in the clinical practice setting. Thus, it is essential to ensure anti-Xa monitoring is utilized appropriately for select patient populations to dissuade unnecessary monitoring of these expensive laboratory markers.

One of the earliest and most essential aspects of therapeutic drug monitoring (TDM) is the appropriate and accurate measurement of drug concentrations in clinical practice.^{18,19} A correctly timed peak anti-Xa level should be drawn approximately 4 hours post dose and after the drug has reached steady state concentrations.^{10,17,20-23} Samples drawn too early or too late should not be utilized to predict enoxaparin activity, because they are less likely to reflect an accurate degree of anticoagulation when correlated with validated target anti-Xa concentrations. Consequently, a clinician may unnecessarily adjust the enoxaparin dose, potentially resulting in enhanced thrombosis or bleeding.

A number of studies have concluded that tests for TDM may be incorrectly performed, sometimes leading to inappropriate clinical decisions or the need for repeat TDM testing.^{18,24-31} To date, there are no studies that primarily identify and describe the practicability of enoxaparin TDM in the literature. Herein, we describe the effectiveness and accuracy of anti-Xa monitoring for patients receiving treatment doses of enoxaparin in the acute care, hospital setting.

METHODS

Study Design, Setting, and Patient Population

This was a retrospective, single-center, cohort study at Upstate University Hospital, a 472-bed tertiary care, level-1 trauma, academic medical center located in Syracuse, New York. Patients were identified via a laboratory-generated report consisting of patients receiving enoxaparin with at least one anti-Xa level obtained from December 1, 2014 to December 31, 2015. Patients were then reviewed through the electronic medical record for pertinent information.

This study was granted exemption status by the institutional review board at Upstate Medical University.

Patients were included if they were at least 18 years of age with an anti-Xa level obtained while on treatment doses of enoxaparin. Treatment doses of enoxaparin were defined as the following based on actual body weight (ABW): 1 mg/kg subcutaneously (SC) every 12 hours or 1.5 mg/kg SC every 24 hours.²¹ Doses were rounded to the nearest available syringe size (ie, 77 mg was rounded to 80 mg doses). Exclusion criteria included patients who were pregnant, on prophylactic dosing, end-stage renal disease (ESRD) on hemodialysis, or if the anti-Xa level was obtained while outpatient at the anticoagulation clinic. Our laboratory utilizes Liquid Anti-Factor Xa 8 kit (Diagnostica Stago, Parsippany, NJ) calibrated with LMWH for anti-Xa analysis.

Anti-Xa concentrations typically peak approximately 4 hours post dose, but peaks can occur anywhere from 3 to 5 hours.^{10,20-23,32,33} Additionally, anti-Xa levels should be measured at steady state concentrations. The half-life of enoxaparin is approximately 4.5 to 7 hours, and steady state is achieved after 4 to 5 half lives.²¹ Based on this information, steady state for enoxaparin is typically and reliably achieved after 3 doses of 1 mg/kg every 12 hours or 2 doses of 1.5 mg/kg every 24 hours. This concentration provides the greatest association with anticoagulant activity, and anti-Xa levels should therefore be obtained within this set time frame.³³ Thus, the definition of correctly drawn anti-Xa concentrations included patients meeting all of the following criteria: treatment doses of enoxaparin as previously described above and collection of blood samples for anti-Xa concentrations 3 to 5 hours post dose at steady state concentrations. At our institution, anti-Xa concentration target ranges are defined as 0.5 to 1.0 IU/mL for every 12-hour dosing and 1.0 to 2.0 IU/mL for every 24-hour dosing, although there have been variable ranges defined in the literature.³⁴ Dose adjustments were made based on a nomogram created and used by Monagle and colleagues if needed.³⁵

Data Collection

Data were extracted by a single reviewer from the electronic medical record using a standardized data collection tool. The following baseline patient demographics were collected: age, gender, height, and weight. Laboratory data were collected on the date of anti-Xa level obtainment. Creatinine clearance,

using ideal body weight and the Cockcroft-Gault equation,³⁶ as well as body mass index (BMI) were calculated based on demographic and laboratory data. Information regarding enoxaparin included dose, frequency, indication, and administration time. The following information was also obtained: indication for anti-Xa measurement, order time, ordering practitioner, collection time by nursing personnel, dose of enoxaparin for which the anti-Xa level was measured, resultant anti-Xa level, and whether a dose adjustment was made based on the resultant level.

Outcomes

The primary objective of this study was to determine the frequency of incorrectly measured anti-Xa levels for patients receiving treatment doses of enoxaparin. Secondary objectives were to determine the number of dose adjustments made based on incorrectly drawn anti-Xa levels as well as the incidence of repeat pharmacodynamic monitoring.

Statistical Analysis

All collected data were entered into a database created with IBM SPSS version 23.0 (IBM Corporation, Armonk, NY) and statistical analyses were performed. Descriptive statistics, including *n* (%) for nominal data, mean $\pm$ standard deviation (*SD*) for normally distributed continuous data, and median (range) for non-normally distributed continuous data were utilized.

RESULTS

Patients

During the study period between December 1, 2014 and December 31, 2015, 203 patients with an anti-Xa level while on treatment doses of enoxaparin were identified. After inclusion and exclusion criteria were applied, 59 patients with a total of 74 anti-Xa levels were analyzed as illustrated in Figure 1. Demographic characteristics are depicted in Table 1. Of note, the median BMI was 30.9 kg/m² (26.1-41.8), which is considered obese according to the obesity classification system.³⁷

Enoxaparin and Anti-Xa Monitoring

Data regarding enoxaparin dose, frequency, and indication as well as anti-Xa monitoring characteristics are represented in Table 2. The mean dose was 1.04 mg/kg, and the majority of patients were on dosing every 12 hours. Various indications for enoxaparin use included deep venous thrombosis

Figure 1. Anti-Xa concentrations included in analysis.

Table 1. Patient demographics (*N* = 59)

Characteristic	<i>n</i> (%)
Mean age, years, $\pm$ <i>SD</i>	63.6 $\pm$ 18.2
Male, <i>n</i> (%)	42 (56.8)
Median weight, kg (range)	87.3 (48.1-229.5)
Median BMI, kg/m ² (range)	30.9 (17.2-84.2)
Median Scr, mg/dL (range)	0.85 (0.40-2.70)
Median CrCl, mL/min (range)	67.3 (12.0-120) ^a

Note: BMI = body mass index; CrCl = creatinine clearance; Scr = serum creatinine. ^aCrCl capped at 120 mL/min.

(DVT), pulmonary embolism (PE), and atrial fibrillation (AF). Most patients met criteria for anti-Xa monitoring due to advanced age. The patients who met multiple criteria were those who were ≥ 75 years old with a CrCl ≤ 30 mL/min; as age increases, CrCl decreases according to the Cockcroft-Gault equation.³⁶ Less than half of all anti-Xa levels in this study were within the defined therapeutic range.

Outcomes

The result of our primary objective in this study is illustrated in Figure 2. Approximately 77% of anti-Xa concentrations collected were drawn incorrectly based on our methodology and definition. The secondary objective of this study is depicted in Figure 3. There were a total of 12 dose adjustments made and 5 of these were implemented based on incorrectly drawn criteria. Additionally, a total of 15 repeat anti-Xa samples were collected due to incorrectly drawn anti-Xa concentrations initially. Approximately 45%

Table 2. Enoxaparin and anti-Xa monitoring characteristics (*N* = 74)

Characteristic		<i>n</i> (%)
Mean dose, mg/kg, $\pm$ SD		1.0 $\pm$ 0.2
Frequency	Every 24 hours	7 (9.5)
	Every 12 hours	67 (90.5)
Indication for enoxaparin	Atrial fibrillation	30 (40.5)
	Deep venous thrombosis	24 (32.4)
	Pulmonary embolism	15 (20.3)
Indication for anti-Xa level	≥ 75 years old	21 (28.4)
	Weight ≥ 150 kg	13 (17.6)
	CrCl ≤ 30 mL/min	7 (9.5)
	Multiple criteria	6 (8.1)
	Did not meet criteria	27 (36.5)
Pharmacist ordered		37 (50)
Anti-Xa level in range		33 (44.6)
Repeat anti-Xa levels performed		15 (20.3)

Note: CrCl = creatinine clearance.

Figure 2. Correctly drawn anti-Xa levels based on defined criteria: anti-Xa level drawn 3-5 hours post dose during steady state concentrations (after the third dose of every 12 hour dosing or after the second dose of every 24 hour dosing).

(33/74) of anti-Xa levels were within the defined range based on the respective dosing strategy. Out of the 33 anti-Xa levels that resulted within the defined range, 10 (roughly 30%) were correctly drawn.

Figure 3. Dose adjustments based on anti-Xa level: anti-Xa level drawn 3-5 hours post dose during steady state concentrations (after the third dose of every 12 hour dosing or after the second dose of every 24 hour dosing).

DISCUSSION

To our knowledge, our study is the first to primarily quantify the frequency of erroneous enoxaparin anti-Xa monitoring. In this study, we clearly found that a substantial number of anti-Xa concentrations were not drawn according to generally accepted recommendations. Approximately 77% (57/74) of anti-Xa levels were drawn either outside the 3- to 5-hour post-dose target time window or drawn prior to steady state concentrations. Furthermore, approximately 41% (5/12) of dose adjustments in this study were implemented based on incorrectly drawn anti-Xa levels.

One of the most essential aspects to TDM in clinical practice is the appropriate obtainment of drug or drug target serum concentrations.^{18,24-31} Incorrectly drawn anti-Xa levels have several important clinical implications. First, clinicians may be unaware that these are drawn inappropriately and interpret these levels as is. This has the potential to lead to patient harm with either a higher or lower subsequent dose adjustment then needed, thus compromising the anticoagulation efficacy and safety of enoxaparin. Even though there are no standardized methods for adjusting enoxaparin doses based on anti-Xa levels other than the nomogram provided by Monagle and colleagues,³⁵ it is still essential to ensure that reasonable

and logical clinical dose adjustments are implemented if needed. Second, incorrectly drawn anti-Xa levels may result in repeat collections to enhance accuracy of this pharmacodynamic parameter. There were a total of 15 repeat anti-Xa levels. At our institution, each patient is charged approximately \$288 per anti-Xa assay, which includes the cost of the assay, the cost of performing the assay, and a predetermined mark up. This is largely associated with a considerable amount of excess patient charges, totaling over \$4,000 in repeat anti-Xa assays in this study. This laboratory test is expensive, and it is important to be able to utilize the result to guide dosage adjustments. It is also important to consider the potential inconvenience and discomfort to the patient with drawing of repeat blood samples. Last, it is important to reassess the indication for enoxaparin anti-Xa monitoring for selected patients since enoxaparin displays predictable pharmacokinetics and pharmacodynamics in the majority of stable, uncomplicated adult patients. This may also decrease the number of inappropriate anti-Xa levels that are ordered initially by clinicians.

There have been numerous studies in the literature describing implications and issues with TDM of other agents in clinical practice. Levine and colleagues performed a retrospective analysis to determine the association between weight-based enoxaparin use and frequency of therapeutic anti-Xa concentrations.³³ However, the authors failed to find an association between weight-based enoxaparin use and attainment of therapeutic anti-Xa concentrations. The authors found that many anti-Xa concentrations were drawn outside current monitoring recommendations, and their criteria for correct measurement of anti-Xa concentrations was the same as in our study. One of their major conclusions was that anti-Xa levels are often drawn incorrectly in clinical practice, yet this was not one of their objectives in their study but rather a significant limiting factor to their sample size. This study by Levine and colleagues suggests that similar issues exist regarding inaccurate obtainment of anti-Xa concentrations in the clinical practice setting.

Based on our findings, it is important to re-educate health care prescribers and nursing personnel on anti-Xa monitoring for enoxaparin as well as to identify mechanisms to improve potential logistical constraints. Perhaps the current process of enoxaparin anti-Xa monitoring is inadequate and alternative strategies may need to be considered.

Limitations

Our study has important limitations to consider. First, it was performed at a single center and there were a limited number of patients included, therefore our results may not be generalizable to other institutions or settings. Second, this study was retrospective in nature, and we acknowledge the related limitations. However, our study design was similar to others that investigated pitfalls with TDM. We believe that a prospective study may have provided a falsely elevated number of correctly drawn anti-Xa levels and a retrospective design for our study objectives more closely aligns with true clinical practice. Other institutions may utilize a different definition of a correctly obtained anti-Xa concentration, which may alter the results from our study. However, there are several aforementioned studies throughout this article that have used similar definitions.

Conclusion

Anti-Xa concentrations are frequently drawn incorrectly in the clinical practice setting and dose adjustments are often made based on these levels. This has the potential to compromise patient safety. Future studies are warranted to confirm the results from our study and to enhance the effectiveness of current TDM practices for enoxaparin.

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