RESEARCH

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Evaluation of Anti-Factor Xa Level Usage for Low Molecular Weight Heparin in a Healthcare System

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ABSTRACT

Background: Low-molecular-weight heparin (LMWH) is a commonly used anticoagulant for treatment of venous thromboembolism (VTE). Routine monitoring of therapeutic effects through anti-Xa levels is not recommended but may be beneficial in patients with altered pharmacokinetics (Cuker, 2018; Garcia, 2012). Inappropriate monitoring leads to excessive testing and premature dose adjustments, compromising safety and efficacy. The purpose of this project was to assess appropriateness of monitoring LMWH anti-Xa levels and identify opportunities to optimize utilization within a community health system.

Methods: A random-sample, retrospective chart review at a multi-site hospital system was conducted over a 3-year period. Inclusion criteria were adults admitted with at least one anti-Xa level resulted. Primary outcomes consisted of anti-Xa level indication and corresponding dose adjustments. Secondary outcomes included anti-Xa levels ordered at the appropriate time window and incidence of adverse events after dose adjustments.

Results: Only 28% (61/220) of patients reviewed had an appropriate indication for LMWH anti-Xa level monitoring. Of the 49 patients warranting dose adjustments, 92% received appropriate adjustments. Anti-Xa levels were drawn after the third therapeutic dose in 146 patients with 84 drawn three to five hours post-dose. Four patients had documentation of bleeding and one patient had thrombosis following inappropriate dose adjustments, compared to no reported events following appropriate adjustments.

Conclusions: Appropriate LMWH anti-Xa monitoring in patients with altered pharmacokinetics resulted in justified dose adjustments and ensured therapeutic concentrations were attained. In patients with appropriate monitoring and dose adjustments, no adverse events were noted. These results will be used to develop a LMWH anti-Xa level monitoring protocol utilizing a multi-disciplinary approach.

Keywords: Pharmacy, LMWH, anticoagulants, LMWH anti-Xa levels, venous thromboembolism

INTRODUCTION

Due to its favorable pharmacokinetic characteristics, low-molecular-weight heparin (LMWH) is widely used in the prevention and treatment of deep vein thrombosis (DVT) and treatment of pulmonary embolism (PE) (Kufel, 2017; Sacha, 2016). LMWHs are anticoagulants that work through inhibition of factor Xa which prevents the conversion of fibrinogen into fibrin, thereby preventing the formation of a clot (Mulloy, 2016). Per the 2018 American Society of Hematology guidelines, routine monitoring of its therapeutic effects through anti-Xa levels is not recommended (Cuker, 2018). If level monitoring is needed, anti-factor Xa assays are the gold standard for assessing therapeutic levels (Wu, 2020). The anti-Xa assay is a chromogenic assay measuring the

total anticoagulant concentration inhibiting factor Xa. Anti-Xa assays utilize a standard curve specific to the anticoagulant being monitored and determine the degree of factor Xa inhibition through cleavage of chromophores off synthetic substrates (Kufel, 2017). These assays may be used for any anticoagulant exhibiting factor Xa inhibition including LMWH, unfractionated heparin (UFH), and direct oral anticoagulants (DOACs). However, as these assays are chromogenic, each assay must be calibrated for the intended anticoagulant (Wei, 2015).

Evidence suggests monitoring anti-Xa levels for LMWH is primarily beneficial in patients who may have altered pharmacokinetics including prolonged half-life, delayed renal elimination, and alterations in bioavailability (Garcia, 2012). This primarily affects patients who are pregnant, extremes of weight including weights of less than 50 kilograms or greater than 150 kilograms, or have renal dysfunction defined as a CrCl of less than 30 mL/min (Sacha, 2016; Wu, 2020). Levels may be utilized to adjust anticoagulant dosing to ensure therapeutic levels are achieved or to prevent adverse effects, such as bleeding or thrombosis due to non-therapeutic concentrations. The goal anti-Xa level for LMWH ranges from 0.6 – 2.0 units/mL, depending on the dosing and/or frequency of LMWH (Garcia, 2012). For patients receiving enoxaparin 1 mg/kg subcutaneously every 12 hours, the recommended therapeutic range is 0.6-1 units/mL. For patients receiving enoxaparin 1.5 mg/kg subcutaneously every 24 hours the recommended therapeutic range is 1-2 units/mL (Garcia, 2012). The appropriate measurement of anti-Xa peak levels constitutes one of the most important aspects of therapeutic drug monitoring. After the drug has reached steady-state concentration following the third or fourth therapeutic dose, the level should be drawn approximately four hours following the dose to measure the maximum anti-Xa activity (Kufel, 2017; Sanofi-Aventis, 2022). Inappropriate monitoring may result in increased costs, avoidable laboratory testing, and unnecessary or incorrect dose adjustments (Kufel, 2017).

The goal of this retrospective research study was to assess the usage and appropriateness of monitoring anti-Xa levels for LMWH within a community health system. The data gathered from this review was used to identify opportunities to optimize ordering trends within the health system.

METHODS

This was an IRB-reviewed, random-sample, retrospective chart review conducted within a large healthcare system in South Florida. Inclusion criteria consisted of patients 18 years and older admitted to a system hospital between August 2018 and September 2021. Patients were included in the analysis if at least one anti-factor Xa level was ordered and resulted for any indication. The patient list was obtained through informatics system reporting of all anti-Xa assays ordered within the health system for the prespecified three-year time period. A retrospective chart review of all patients with an anti-factor Xa level was conducted to determine which anticoagulant the patient had received. No exclusion criteria were considered for this review. Using Microsoft Excel, a cohort of patients was randomly selected for analysis. All data were de-identified and stored in an encrypted, secured database.

Primary outcomes included the percent of patients with an appropriate indication for anti-Xa level monitoring and the percent of patients who received appropriate anticoagulant dose adjustments depending on the resulting level, if applicable. An appropriate indication was defined as monitoring for pregnant patients, those with a weight of $\leq$ 50 kg or $\geq$ 150 kg, patients with a CrCl $\leq$ 30 mL/min, or those that experienced an incidence of bleed or thrombosis while receiving therapeutic doses of LMWH (Sacha, 2016). An additional appropriate indication, monitoring for patients continuing non-standard doses of LMWH, was included to account for patients admitted with outpatient use of enoxaparin at doses other than 1 mg/kg twice daily or 1.5 mg/kg once daily to ensure therapeutic concentrations were attained. As there is a lack of recommended guidelines for LMWH dose adjustments based on anti-Xa levels, an appropriate dose adjustment was defined as any dose increase or decrease following an appropriately drawn subtherapeutic or supratherapeutic level, respectively.

Secondary outcomes included the percentage of levels drawn within the appropriate time window and the incidence of bleeding or thrombosis following inappropriate dose adjustments. An appropriate time window was defined as three to five hours following a dose of LMWH, as well as levels drawn following at least the third therapeutic dose of LMWH. Data points collected included the anticoagulant agent, dose, indication, and administration time; indication for anti-Xa

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level monitoring, and anti-Xa sample collection time relative to the dose of the anticoagulant given. Data were collected to assess if the dose was appropriately adjusted in patients who received an anticoagulant dose adjustment following anti-Xa level monitoring. Patient baseline characteristics collected included creatinine clearance (mL/min), weight (kg), and COVID-19 status as COVID-19 predisposes patients to a hypercoagulable state and may result in a greater number of patients receiving anticoagulation (Singhania, 2020). Descriptive statistics were used for analysis of patient baseline characteristics, primary outcomes, and secondary outcomes.

RESULTS

Over a three-year period, 441 anti-Xa levels were ordered for 282 patients within the health system. A total of 220 patients were randomly selected for analysis. Patients included in the analysis had a mean CrCl of 59 mL/min, mean weight of 90 kg, and 107 patients (49%) had a current diagnosis of COVID-19 (Table 1). Anti-Xa assays available within the health system are only calibrated for use with LMWH, however, 6.4% of patients with anti-Xa monitoring received treatment with an anticoagulant other than LMWH and 24.3% (50/206) of patients received prophylactic dosing of LMWH. The primary indications for therapeutic anticoagulation were DVT (24%) and PE (24%).

Approximately 28% (n=61) of patients had an appropriate indication for anti-Xa level monitoring (Table 2). The most common appropriate indications were extremes of weight (31%, n=19), renal impairment (25%, n=15), and active bleed while receiving treatment with LMWH (25%, n=15). For the 156 patients (71%) on therapeutic doses of LMWH, 45 of 49 patients (92%) received appropriate dose adjustments following anti-Xa level monitoring (Figure 3).

Secondary outcomes included an assessment of levels drawn at the appropriate time window and incidence of bleed or thrombosis after inappropriate dose adjustments, shown in Figure 2 and Table 4, respectively. Anti-Xa levels were drawn after the third therapeutic dose of LMWH in 146 patients and 84 of these patients had levels drawn three to five hours post-dose (Figure 2). Therefore, 54% of levels drawn were within the appropriate time frame. A total of four patients had adverse events of bleeding and one patient had an event of thrombosis following inappropriate dose adjustments compared to no adverse events documented in patients who received appropriate dose adjustments.

DISCUSSION

The results of this retrospective study have shown appropriate monitoring of anti-Xa levels for LMWH may be associated with a decreased incidence of adverse events. No incidences of bleeding or thrombosis were documented for the 45 patients with appropriate dose adjustments; however, adverse events occurred in five patients following inappropriate dose adjustments.

Inappropriate indications for anti-Xa level monitoring predominantly consisted of indications that evidence suggests is of little to no benefit (Table 3). The most common inappropriate indication was confirming the appropriateness of LMWH dose (60%). These patients did not have any of the pre-determined appropriate indications and did not have documentation to suggest evidence of altered pharmacokinetics. Other cases of inappropriate monitoring included patients with an appropriate indication listed, however, the patient did not meet the pre-specified cut-off criteria. For example, renal impairment was documented as the indication for two percent of patients, however, these patients had a CrCl > 30 mL/min and did not have evidence of acute kidney injury (AKI).

As described previously, anti-Xa assays for anticoagulants other than LMWH were not available for ordering within the health system. Limited data has been published on the use of anti-Xa assays calibrated for a different anticoagulant. This use may result in less accurate results which cannot be inferred quantitatively for appropriate dose adjustments (Kufel, 2017). Of the 14 patients who had LMWH-calibrated anti-Xa monitoring while receiving treatment with another anticoagulant, some may possibly have had levels drawn due to misinterpretation of the assays available within the health system. The specific name for the lab order within the electronic health system stated “Anti-Xa LMW Heparin”. Following results of this retrospective chart review, the lab order name was modified to “Anti-Xa LMWH (enoxaparin)” to decrease incidences of monitoring for incorrect anticoagulants.

The economic impact of anti-Xa level monitoring is a factor that must be considered as well.

Each LMWH anti-Xa level has an estimated cost of $200 to $300 per level and varies per institution (Kufel, 2017). Untimely and inappropriate monitoring may lead to excessive testing resulting in increased laboratory costs.

Limitations

There were several limitations to this review. First, this was a retrospective study within one health system which may limit applicability to other populations. Second, part of this study was conducted during the COVID-19 pandemic. Approximately 49% of patients had a diagnosis of COVID-19 which predisposes patients to a hypercoagulable state and may have resulted in more levels ordered in this population. Lastly, the inconsistent documentation of indication impacted the assessment of 32% of patients with an anti-Xa level drawn. These patients did not have an indication for monitoring stated and did not have one of the pre-determined appropriate indications.

CONCLUSION

In conclusion, appropriate anti-Xa level monitoring resulted in justified LMWH dose adjustments to ensure therapeutic concentrations were attained in patients with potential altered pharmacokinetics. In patients who received appropriate monitoring and subsequent appropriate dose adjustments, there were no adverse events noted. Overall, the results of this study show that further education for the appropriate utilization of anti-Xa assays may be necessary to prevent adverse events associated with inappropriate dose adjustments. The results of this retrospective research study will be shared with pertinent stakeholders to develop a multi-disciplinary protocol for monitoring LMWH anti-Xa level.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Table 1

*Baseline Characteristics (*N=*220)*

Characteristics	*n*
Creatinine clearance, mean (mL/min)	59
Weight, mean (kg)	90
COVID-19, n (%)	107 (49)
Anticoagulant, *n* (%)	
o Enoxaparin (therapeutic)	156 (71)
o Enoxaparin (prophylaxis)	50 (23)
o Direct oral anticoagulant (DOAC)	8 (4)
	6 (3)
Anticoagulant indication, *n* (%):	
o Deep vein thrombosis (DVT)	53 (24)
o Pulmonary embolism (PE)	53 (24)
o DVT and PE	31 (14)
o Atrial fibrillation	11 (5)
o Venous thromboembolism prophylaxis	52 (24)
o Other	20 (9)
Anticoagulant switch post anti-Xa level, *n* (%)	8 (4)

Table 2

Appropriate Indication for Anti-Xa Level Monitoring

Indication for Appropriate Anti-Xa Level	Number of Patients (%) *n*=61
Weight extreme	19 (31)
Renal impairment	15 (25)
Active bleed	15 (25)
Thrombosis	8 (13)
Assess appropriateness of non-standard dose	2 (3)
Pregnancy	2 (3)

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Table 3

Inappropriate Indications for Anti-Xa Level Monitoring

Documented Anti-Xa Level Indication	Number of Patients (%) *n*=88	Reason Indication Not Appropriate
Confirming appropriateness of dose	53 (60)	Not an approved indication
Heparin or DOAC	14 (16)	Wrong medication
Weight extreme	8 (9)	Weight between 51 kg and 149 kg
Bleed risk	7 (8)	Risk unverified
Preparation for discharge	2 (2)	Not an approved indication
Renal impairment	2 (2)	CrCl > 30 mL/min
CHF exacerbation	1 (1)	Not an approved indication
Possible HIT	1 (1)	Not an approved indication

Note: DOAC, direct oral anticoagulant; CHF, congestive heart failure; HIT, heparin-induced thrombocytopenia

Table 4

*Adverse Events Following Dose Adjustments (*n=*66)*

	Adverse Events	
	After Appropriate Dose Adjustments (*n*=45)	**After Inappropriate Dose Adjustments (*n*=21)**
Bleed, *n* (%)	0 (0)	4 (19)
Thrombosis, *n* (%)	0 (0)	1 (5)

Figure 1

*Appropriateness of Anti-Factor Xa Level Indication (*N=*220)*

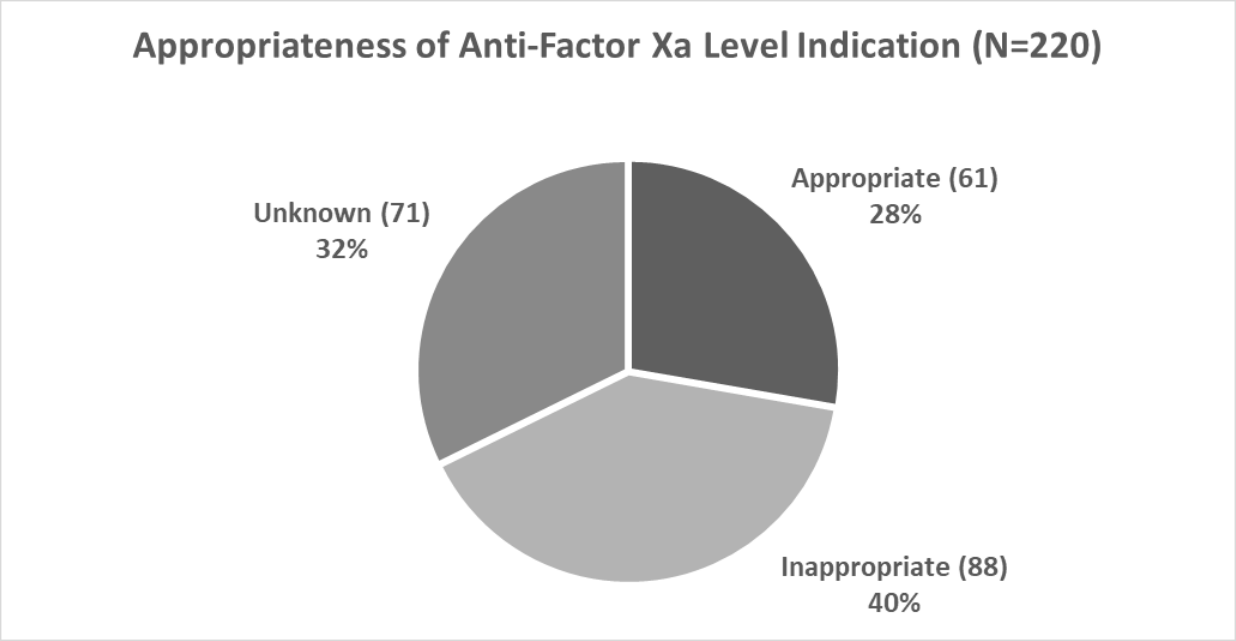

Figure 2

Appropriate Enoxaparin Anti-Xa Level Timing

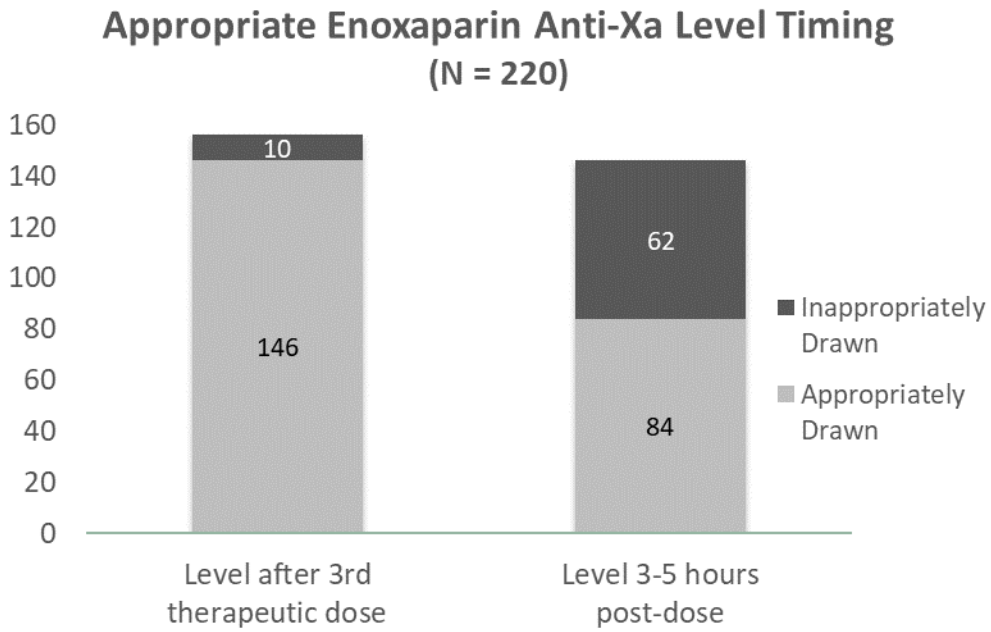

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Figure 3

Dose Adjustments Following Anti-Xa Level Monitoring