Enoxaparin Dosing and AntiXa Monitoring in Specialty Populations: A Case Series of Renal-Impaired, Extremes of Body Weight, Pregnant, and Pediatric Patients

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ABSTRACT

The use of enoxaparin in specialty populations—including those with renal dysfunction, extremeness of body weight, pregnant patients, and pediatric patients—has not been studied in clinical trials. Monitoring anti-factor Xa activity (antiXa) as a surrogate to measure the activity of enoxaparin may be of interest. A case series of patients admitted to New York University Langone Health between December 2012 and July 2014 who received at least three consecutive doses of enoxaparin for the treatment of VTE and had a peak antiXa level drawn at steady state were evaluated. Patients were included if they were ≤ 18 years of age or if they were > 18 years of age *and* met one of the following criteria: pregnant, creatinine clearance (CrCl) ≤ 50 ml/min at the time of initiation of enoxaparin, or had a body weight ≤ 50 kg or ≥ 120 kg. A total of 31 patients were included in the analysis. The percentage of patients who achieved a therapeutic antiXa level (0.5–1.2 IU/mL for twice daily enoxaparin or 1–2 IU/mL for once daily enoxaparin) at the time of the first antiXa level drawn was greatest for the adult patients; however, the patients with renal impairment and low body weight were more likely to be sub-therapeutic at first antiXa level check. In addition, neonates and young children required increased enoxaparin doses to achieve therapeutic antiXa. Optimal dosing of enoxaparin in specialty populations has not been established. Furthermore, higher initial doses of enoxaparin may be needed in pediatric patients to attain therapeutic antiXa levels.

Keywords: Enoxaparin, specialty populations, therapeutic drug monitoring, antifactor Xa, antiXa, pediatric, low-molecular-weight heparin

INTRODUCTION

Although information regarding the incidence of venous thromboembolism (VTE) is limited, the CDC estimates an incidence of 300,000 to 600,000 VTE events annually.[1] These estimates may be an underestimate, as VTE can be missed or misdiagnosed, along with low autopsy rates for fatal pulmonary embolism.[1] Although less common, pediatric VTE has become an emerging problem with an estimated 70% increase in incidence of annual VTE events from 2001 to 2007 in hospitalized children.[2]

Major risk factors for VTE in adult patients include morbid obesity, acute medical illness, hormonal changes during pregnancy, or the presence of central venous catheters.[3-5] In pediatric patients, risk factors are not well defined; however, adolescence, obesity, leukemia, and presence of central venous catheters have been associated with higher risk in younger pediatric patients.[6-8] Paradoxically, the optimal treatment of VTE in specialty patient populations, such as pediatric patients, those with morbid obesity, low body weight, kidney disease, and pregnant patients, is uncertain. In the general population, low molecular weight heparins (LMWHs) such as enoxaparin have become favored over unfractionated heparin (UFH) due to predictable pharmacokinetic properties, decreased need for monitoring laboratory parameters, convenience of dosing, and a decreased incidence of adverse events. Enoxaparin is indicated for the treatment and prevention of VTE and acute coronary syndrome. According to the American College of Chest Physicians, enoxaparin is equivalent to UFH for the treatment of patients with VTE including deep vein thrombosis (DVT) and pulmonary embolism (PE).[9-11]

The majority of enoxaparin studies have excluded specialty patient populations such as those who were renal-impaired or pregnant; pediatric patients; and those with extremes of body weight. Enoxaparin, which is primarily eliminated by the kidneys, may have bioaccumulation in the presence of renal insufficiency, and thus may precipitate or potentiate bleeding episodes.[12] Observational data as well as pharmacodynamic data suggest that patients with moderate renal impairment, defined as creatinine clearance of 30–50mL/min, may be at an increased risk for bleeding events with supratherapeutic antiXa levels.[13] Furthermore, although subcutaneous administration of enoxaparin results in close to 100% bioavailability in the general population, with a volume of distribution similar to that of plasma, there is concern that there may be bioaccumulation in obese patients.[14] For pregnant patients, as maternal weight changes, the activity of enoxaparin may need to be monitored through antiXa, although data to support dose adjustments based on this are conflicting.[15-17] Higher doses of enoxaparin may be needed in pediatric patients to target a peak antiXa between 0.5 and 1.0 IU/mL, although enoxaparin has not been studied extensively in this population.[8, 18]

Enoxaparin does not typically require routine laboratory

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Disclosures: The authors report no commercial or financial interests in regard to this article.

Table 1 Baseline Characteristics of Study Patients

	Age ≤ 18 (n = 11)	CrCl < 30 mL/min (n = 3)	CrCl 30–50 mL/min (n = 5)	ABW ≤ 50 kg (n = 7)	ABW ≥ 120 kg (n = 2)	Pregnant (n = 3)
Age (years), median (range)	0.5 (0–18)	83 (80–89)	85 (68–88)	80 (48–89)	63 (55–71)	35 (29–39)
Sex (female)	6 (54)	3 (100)	5 (100)	2 (29)	1 (50)	3 (100)
Baseline CrCl (mL/min)[1], median (range)	122 (26–1008)	26 (24–29)	39 (30–49)	49 (32–184)	123 (68–177)	107 (100–122)
Weight (kg), median (range)	23 (3–57)	48 (39–59)	51 (39–63)	46 (44–49)	128 (124–132)	73 (58–85)
Indication						
DVT	5 (46)	2 (67)	1 (20)	4 (57)	1 (50)	2 (67)
Catheter thrombosis	2 (18)	—	—	—	—	—
PE	2 (18)	—	2 (40)	1 (14)	—	1 (33)
Other (ACS, AFIB, Stroke)	2 (18)	1 (33)	2 (40)	2 (29)	1 (50)	—
Location						
Critical Care/Step Down Units	11	0	1	0	0	1
Medical/Surgical General Floors	0	3	4	7	2	2
Comorbid Condition						
Congenital heart disease	6 (55)	N/A	N/A	N/A	N/A	N/A
Heart failure	—	1 (33)	3 (60)	2 (29)	1 (50)	—
Hepatic insufficiency	—	—	—	—	—	—
Renal insufficiency	1 (9)	3 (100)	5 (100)	4 (57)	—	—
History of cancer	2 (18)	1 (33)	3 (60)	5 (71)	—	—
Obese (BMI > 30)	N/A	—	—	—	2 (100)	1 (33)
Underweight (BMI < 18.5)	N/A	1 (33)	2 (40)	4 (57)	—	—
Concomitant medications						
Warfarin	0	1	3	2	1	0
Ibuprofen	1	0	0	1	0	1
Aspirin	1	1	2	1	0	1

[1]CrCl based on Bedside Schwartz Equation for Age ≤ 18 and Cockcroft-Gault Equation for all others.
All values represented as n (%) unless specified.

ABW = adjusted body weight; ACS = acute coronary syndrome; AFIB = atrial fibrillation; BMI = body mass index; CrCL = creatinine clearance; DVT = deep vein thrombosis; N/A = not applicable; PE = pulmonary embolism.

monitoring in most patients, compared to UFH. However, monitoring antiXa activity as a surrogate in specialty patient populations, including those with renal dysfunction, extremes of body weight, and in pediatric patients, may be of interest to ensure the drug is achieving the desired activity.[12, 19] Because enoxaparin is a mixture of longer and shorter glycosaminoglycan fragments, serum drug concentrations are not measurable.[19] However, the pharmacokinetics of enoxaparin can be determined based on anticoagulation activity measured by a calibrated antiXa assay.[19] Previous clinical trials evaluating enoxaparin did not target antiXa levels to guide dosing and most of the data regarding antiXa monitoring has been determined retrospectively. As part of a quality assessment, we sought to evaluate our own institutional recommendation to monitor a peak antiXa level 3 to 5 hours post-dose, once at steady state, in these specialty populations to guide in optimal enoxaparin dosing.

METHODS

This was a single-center, retrospective review conducted at New York University Langone Health (NYULH), a 825-bed tertiary care academic teaching hospital. Because of the retrospective nature of this observational review for quality assurance purposes, informed consent was not required. All patient data was de-identified and collected in compliance with the hospital's institutional review board exempt protocols.

Electronic health records of patients who received at least 3 consecutive doses of enoxaparin for the treatment of VTE and had a corresponding peak antiXa level drawn at steady state were reviewed between December 2012 and July 2014. Steady state was defined as antiXa at 3 to 5 hours after the third or fourth dose of enoxaparin. Patients were included if they were ≤ 18 years of age or if they were > 18 years of age and met one of the following criteria: pregnant, creatinine clearance (CrCl) ≤ 50 ml/min at the time of initiation of enoxaparin, or body weight ≤ 50 kg or ≥120 kg. These criteria were chosen, as the antithrombotic therapy oversight committee at our institution suggests monitoring the activity of enoxaparin in these specialty groups. All other patients were excluded.

Data were obtained through a retrospective medical record review of baseline demographics, enoxaparin dosing regimens, antiXa measurements, incidence of adverse events including

Table 2 Primary and Secondary Outcomes

Primary Outcome	Age ≤ 18 (n = 11)	CrCl < 30 mL/min (n = 3)	CrCl 30–50 mL/min (n = 5)	ABW ≤ 50 kg (n = 7)	ABW ≥ 120 kg (n = 2)	Pregnant (n = 3)
Anti-Xa at First Level:						
Therapeutic[1]	1 (9)	1 (33)	2 (40)	4 (57)	2 (100)	2 (67)
Sub-Therapeutic	9 (82)	2 (67)	3 (60)	3 (43)	—	1 (33)
Supra-Therapeutic	1 (9)	—	—	—	—	—
Secondary Outcomes	**Age ≤ 18 (n = 11)**	**CrCl < 30 mL/min (n = 3)**	**CrCl 30–50 mL/min (n = 5)**	**ABW ≤ 50 kg (n = 7)**	**ABW ≥ 120 kg (n = 2)**	**Pregnant (n = 3)**
Anti-Xa Level at 7 days:						
Therapeutic[1]	9 (82)	1 (33)	3 (60)	4 (57)	2 (100)	2 (67)
Sub-Therapeutic	2 (18)	2 (67)	2 (40)	3 (43)	—	1 (33)
Supra-Therapeutic	—	—	—	—	—	—
# of Dose Adjustments to Reach Therapeutic Range, mean (range)	3 (1–5)	0.5 (0–1)	—	—	1 (0–2)	—
Days to Reach Therapeutic Range, mean (range)	4 (1–8)	7 (1–13)	2 (2–3)	2 (1–3)	5 (2–7)	3 (2–4)
Major or Minor Bleeding Events	—	—	—	—	—	—
Incidence of HIT	—	—	—	—	—	—
Progression or Reoccurrence of Thrombosis	1 (9)	—	—	—	—	—

[1] Anti-Xa therapeutic range at our institution is between 0.5 and 1.2 for twice-daily dosing, and between 1.0 and 2.0 for daily dosing.
All values represented as n (%) unless specified.

CrCL = creatinine clearance; HIT = heparin-induced thrombocytopenia.

thrombocytopenia, bleeding, and recurrent thrombotic or bleeding events within 2 weeks of initiation of enoxaparin. Creatinine clearance was estimated using the Cockcroft–Gault equation for adults and the modified Schwartz equation for pediatrics.

Heparin-induced thrombocytopenia (HIT) was assessed through documentation, in the electronic health record (EHR), of suspicion of this clinical diagnosis, along with laboratory confirmation with either the heparin platelet factor 4 (HPF4) antibody or corresponding serotonin release assay (SRA). Major bleeding was defined using the International Society of Thrombosis and Hemostasis criteria: fatal bleeding; a decrease in hemoglobin by 2 g/dL in a 24-hour period; bleeding associated with transfusion of 2 or more units of whole blood, red blood cells, or surgical intervention; symptomatic bleeding in a critical area or organ (intracranial, pulmonary, or retroperitoneum).[20] Minor bleeding was defined as overt bleeding associated with an intervention or discontinuation of therapy that did not meet the criteria for major bleeding.[20]

The primary outcome was the percentage of patients who achieved a therapeutic antiXa at the first level drawn. Therapeutic antiXa was defined as 0.5–1.2 international units/mL for twice daily dosed enoxaparin and 1–2 international units/mL for once daily dosed enoxaparin, as this is the therapeutic range established at our institution. Secondary outcomes included the percentage of patients with antiXa level that were therapeutic at day 7, the mean days it took to reach a therapeutic range, the starting and final dose to achieve a therapeutic antiXa, major or minor bleeding events, or other adverse events, such as thrombocytopenia or suspicion of recurrent thromboembolism as clinician assessment in the EHR or with corresponding imaging studies, within 2 weeks of enoxaparin.

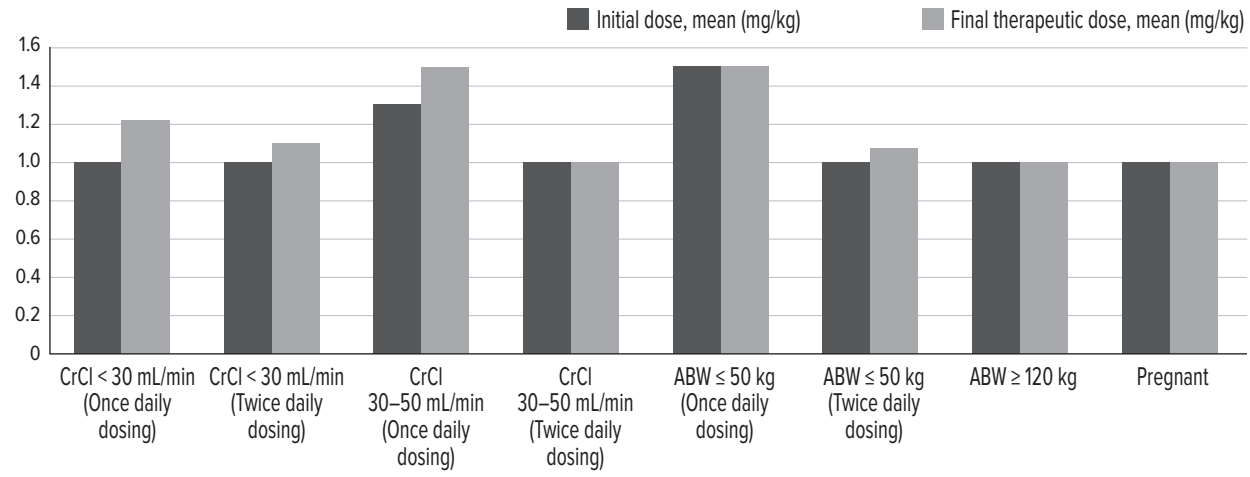
Descriptive statistics were used to analyze the data.

RESULTS

In total, 1,552 patient encounters with enoxaparin administrations were screened (80 pediatric and 1,472 adult patients). Patients were excluded if they received fewer than 3 enoxaparin doses (n = 762), followed by prophylactic-dosed enoxaparin (n = 556). Of the remaining 206 patients, there were 26 pediatric patients, 6 pregnant patients, 24 overweight patients, and 152 patients with CrCl < 50 mL/min. Patients were excluded from analysis if there was no corresponding antiXa drawn at steady state. A total of 31 patients were included in the final analysis.

The median age for each specialty population varied: 6 months (0–18 years) for pediatric patients, 35 years (29–39 years) for pregnant patients, 84 years (80–89 years) for the renal-impaired, 63 years (55–71 years) for obese patients, and 80 years (48–89 years) for those with low body weight. The indication for the majority of the enoxaparin utilized in these specialty populations was VTE, including DVT and PE (Table 1). The percentage of patients who achieved a therapeutic antiXa level (0.5–1.2 IU/mL for twice daily enoxaparin or 1–2 IU/mL for once daily enoxaparin) with the first antiXa level drawn was greatest for the obese patients (100%) followed by pregnant patients (67%), those with low body weight (57%), those who were renal-impaired (33–40%), and lastly, pediatric patients

Figure 1 Starting Dose and Final Dose to Achieve Therapeutic AntiXa Stratified for Adult Patients



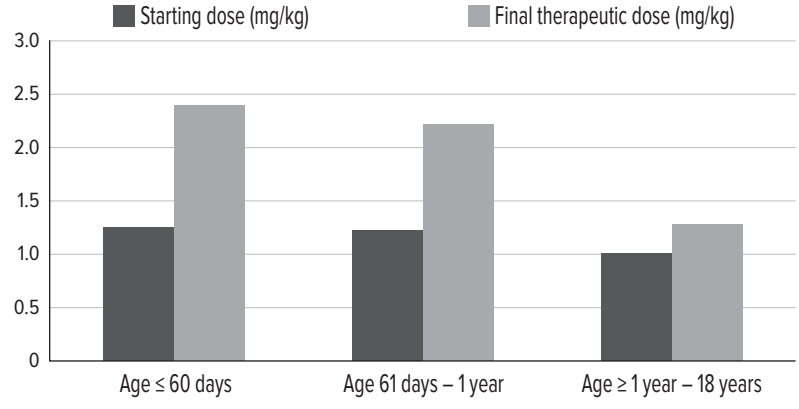
(9%). The pediatric patients' first antiXa was sub-therapeutic in the majority (82%) of cases, followed by the renal-impaired, those with low body weight, and pregnant patients. Only 1 pediatric patient had a supratherapeutic antiXa with the first level drawn (Table 2).

We stratified the starting weight-based dose for adults and pediatric patients. For adults, the initial mean weight-based dose per administration for twice daily dosing was 1.09 mg/kg ± 0.16mg/kg (Figure 1). Although our institution's recommendation for dosing enoxaparin in neonates and children is 1.5mg/kg subcutaneously every 12 hours for children who were < 2 months of age and 1 mg/kg subcutaneously every 12 hours for children > 2 months of age, we noted increased enoxaparin dosing requirement in neonates and young children. We found that pediatric patients younger than 1 year of age in an ICU setting required higher doses (mean of 2.02 mg/kg ±0.65mg/kg every 12 hours for twice daily dosing) and took longer to meet therapeutic goals (mean of 4 ± 2 days). Furthermore, mean weight-based dosing was 1.58mg/kg ± 0.55mg/kg for neonates and 1.4mg/kg ± 0.45mg/kg for children > 2 months of age (Figure 2).

We also aimed to evaluate the percentage of patients who achieved a therapeutic antiXa at day 7 and found that 50% of patients with CrCl <50 mL/min reached a therapeutic peak at a mean of 7 days, with the other 50% of patients remaining sub-therapeutic at 7 days. We only had 3 patients with CrCl < 30mL/min, with 1 patient therapeutic at 7 days and 2 who were subtherapeutic at 7 days.

There were no major or minor bleeding events, thrombocytopenia, or documentation of suspicion for HIT during our study period. We found 1 pediatric patient, age 3 months, to have documentation of suspicion for progression of thrombosis while on enoxaparin. In this patient, enoxaparin was initiated at 1.5mg/kg twice daily with a subtherapeutic antiXa level at first draw. Subsequently, 4 dose adjustments were made and a final dose of 2.75 mg/kg twice daily was necessary to achieve a therapeutic antiXa level of 0.77 units/mL.

Figure 2 Starting Dose and Final Dose to Achieve Therapeutic AntiXa Stratified for Pediatric Patients



DISCUSSION

Overall, monitoring of peak antiXa activity of enoxaparin at steady state in specialty populations was very low at our institution, as demonstrated by our small sample size. These findings are consistent with previous literature and highlight the difficulties in assessing enoxaparin activity in hospitalized patients.[21] Although data on the efficacy and safety of enoxaparin in specialty populations is mainly observational and extrapolated from pharmacokinetic studies, enoxaparin is utilized in these patient groups. Furthermore, although therapeutic antiXa ranges have not been clinically validated, peak antiXa levels, drawn 4 hours following enoxaparin administration have been recommended by a consensus of practitioners.[12, 19]

There is a risk of enoxaparin accumulation and bleeding in patients with renal dysfunction, given the lower molecular

weight and lesser negative charge with greater dependency on renal elimination for clearance.[15] Enoxaparin use in patients with moderate to severe renal impairment (CrCl 30–50mL/min and CrCL <30mL/min) with antiXa monitoring was infrequent at our institution, likely due to the avoidance of medications with renal clearance in patients with renal impairment. In addition, the patients with impaired renal function tended to be elderly, with lower body weights, and were among the least likely to reach therapeutic goal. Dose adjustments were rarely made in these specialty patient populations, despite sub-therapeutic levels, as there may have been concern about bioaccumulation with continued exposure. These results are consistent with previously published literature suggesting that patients with low body weight and renal impairment may have subtherapeutic antiXa levels.[21] In addition, renal insufficiency is a risk factor in and of itself for bleeding with anticoagulation therapy.[22] A pharmacokinetic study of 19 patients (CrCl range, 11.6–29.4mL/min) has suggested that dose-adjusted enoxaparin (1 mg/kg every 24 hours) is associated with achieving a therapeutic peak in 74% of the patients studied, with no major bleeding events noted.[23] Previous studies have suggested CrCl <30 mL/min as the threshold for enoxaparin accumulation and the threshold for when to reduce the dose of enoxaparin to decrease the risk of clinically significant accumulation and bleeding.[24] The American College of Chest Physicians endorses antiXa levels in patients with severe renal insufficiency to minimize bleeding risk.[25] However, there is a lack of consensus regarding the level of renal dysfunction below which there is a risk of accumulation. Some studies suggest that a CrCl of <50mL/min may lead to an accumulation of enoxaparin.[13, 26] At our institution, the antithrombotic therapy oversight committee recommends monitoring antiXa in patients with severe renal insufficiency (CrCl < 30mL/min) and suggests monitoring antiXa in patients with moderate renal impairment (CrCl 30–50mL/min), given concerns about bioaccumulation with prolonged exposure, but does not endorse monitoring antiXa activity in all patients with moderate renal impairment.

Although subcutaneous administration of enoxaparin results in close to 100% bioavailability, with antiXa levels in the expected range for patients weighing up to 144 kg, there is concern that there may be bioaccumulation in obese patients.[19] However, the bleeding risk in this population appears to be low.[13, 27] At our institution, we suggest monitoring peak antiXa in patients with weights > 120 kg or BMI > 35 to ensure peak levels are not supratherapeutic, even though there is limited data to support this practice.[12,19] Two patients in our cohort with body weight > 120 kg at the standard weight-based enoxaparin dose achieved therapeutic antiXa, consistent with what has been previously published.[13] However, given the small sample size, it is difficult to know if this would apply to all obese patients. Further, with prolonged enoxaparin use, there may be a risk of bioaccumulation and some have suggested that monitoring trough antiXa levels may help better predict this risk.[19]

Antithrombotic therapy in pregnant patients is often challenging because of changes in maternal weight and bleeding risks for both the mother and the fetus. Although the data vary with regard to dose adjustments of enoxaparin during pregnancy as maternal weight changes,[6-17, 28-29] our institution suggests monitoring peak antiXa in pregnant patients receiving enoxaparin. As we were not able to assess our pregnant patients throughout gestational progression, it is difficult to draw definitive conclusions; however, we did not find peak antiXa to be affected by pregnancy at standard enoxaparin weight-based dosing, as has been reported.[16] Therefore, we no longer recommend peak antiXa for all pregnant patients. Instead, we suggest monitoring peak antiXa if there are significant changes in maternal weight or if there is prolonged therapeutic enoxaparin use in these patients.

We did not observe adverse effects such as bleeding or thrombocytopenia during treatment with enoxaparin. However, our analysis is limited by its retrospective nature, documentation of such events, and time interval for which we evaluated such events. If prolonged enoxaparin is used in patients with risk for bioaccumulation, such as those with low body weight, who were obese or pregnant, or those with renal impairment, it may be prudent to monitor antiXa activity. More recently, monitoring of trough antiXa instead of peak levels has been recommended to assess for bioaccumulation, which may be valuable in these specialty groups.[19] Of note, we did not assess for patients being 'bridged' to warfarin or the concomitant INR at the time of enoxaparin administration.

The greatest impact that this quality assurance helped us to assess was the need for higher initial doses of enoxaparin in pediatric patients. The unpredictable pharmacokinetics of enoxaparin in pediatric patients appear to be age-dependent.[8] At least two studies have suggested that pediatric populations (specifically, ages 61 days to ≤ 1 year) require higher enoxaparin doses than those currently recommended by CHEST guidelines (1.3 mg/kg every 12 hours vs. 1 mg/kg every 12 hours).[8, 30-31] Our study supports the evidence suggesting higher initial doses of enoxaparin in pediatric patients and the need for institutions to develop protocols to ensure antiXa levels are drawn four hours post-dose at steady state.[8] Interestingly, we did observe one pediatric patient to have suspicion of progression of thrombosis documented in the clinician assessment, however it was unknown if the subtherapeutic antiXa along with the multiple dose adjustments necessary to achieve therapeutic antiXa may have affected the clinician's suspicion. There was no documentation of further progression of thrombosis or evidence of adverse events noted within two weeks after the therapeutic antiXa was achieved. Further prospective studies to determine the most effective initial enoxaparin dose could significantly decrease length of stay and provide better quality of care for pediatric patients.

There are several limitations to our study, including the retrospective design, small sample size, and time period for which we were able to evaluate enoxaparin utilization and adverse events. We sought to review cases of patients hospitalized in specialty groups who had peak antiXa levels monitored with enoxaparin use to understand how enoxaparin is dosed and monitored in these cohorts. However, our sample size was limited due to overall low utilization and low monitoring of peak antiXa, with many subgroups. Even when antiXa levels were monitored, many times the levels were not drawn at steady state, as indicated by the patients we excluded from our review. In addition, despite sub-therapeutic antiXa levels in our moderate and severe renal-impaired population, the doses of enoxaparin were not adjusted because of concerns

about bioaccumulation with time or 'bridge' therapy that we did not assess. Therefore, we cannot say with certainty that these doses are safe for all patients with moderate or severe renal impairment. Our findings highlight the challenges with monitoring peak antiXa levels in hospitalized patients, such as timing of appropriate laboratory assessment.

CONCLUSION

Due to limited retrospective data, the optimal dose of enoxaparin in specialty populations, including those with renal dysfunction, extremes of body weight, pregnant patients, and pediatric patients, has not been established. Surrogate laboratory monitoring of peak antiXa levels may help predict the pharmacokinetics of enoxaparin in these specialty groups; however, the effects on clinical outcomes are unknown. Monitoring trough antiXa instead of peak levels in patients at risk of bioaccumulation, such as prolonged enoxaparin exposure in extremes of body weight or renal impairment may be of greater value.[19] Our study highlights the difficulties in predicting the pharmacokinetics of enoxaparin in these patients and also the difficulty in obtaining antiXa levels in hospitalized patients. Lastly, our findings add to the growing body of evidence suggesting that higher initial doses of enoxaparin are needed in pediatric patients to attain therapeutic antiXa levels.

To further investigate the significance of antiXa monitoring, and how best to utilize this laboratory test to assess the activity of enoxaparin, as well as the clinical validity, we suggest studying enoxaparin antiXa monitoring in larger cohorts of specialty populations.

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