JPPT | Single-Center Retrospective Study

Impact of Pharmacist-To-Dose Enoxaparin in Pediatric Patients

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OBJECTIVE Variations in pharmacokinetics necessitate monitoring anti-Xa concentrations for optimal anticoagulation in pediatric patients receiving enoxaparin for the prophylaxis or treatment of venous thromboembolism. Pharmacists play an essential role through pharmacist-to-dose (PTD) protocols. This study aims to assess the impact of pharmacist involvement by comparing rates of achieving target anti-Xa concentrations before and after implementation of the PTD protocol in a pediatric population.

METHODS Medical records were queried for patients 18 years old and younger who received enoxaparin as an inpatient at West Virginia University Medicine Children's Hospital from January 2016 to September 2023. Indication, dosing, and administration of enoxaparin were assessed. Anti-Xa concentrations were evaluated for appropriate timing and goal range. Secondary outcomes included the number of anti-Xa concentrations drawn, the number of enoxaparin dose adjustments, the rate of accurately drawn anti-Xa concentrations, the rate of following guideline recommended enoxaparin dosing on initiation, and the time to goal anti-Xa concentration.

RESULTS There was no difference in the rate of anti-Xa concentrations that were in goal before and after the implementation of a pharmacist-led enoxaparin dosing protocol. The frequency of concentrations drawn appropriately was higher, and the time to goal was shorter after the implementation of the PTD protocol, although this difference was not statistically significant.

CONCLUSIONS There was no difference in the rate of anti-Xa concentrations that were in goal between groups. This likely stemmed from the use of the same dose adjustment guideline among both groups. This underscores the equal quality of care provided by pharmacists in achieving optimal anticoagulation and positive outcomes.

ABBREVIATIONS eGFR, estimated glomerular filtration rate; PTD, pharmacist-to-dose; VTE, venous thromboembolism

KEYWORDS anticoagulation; enoxaparin; pediatrics; pharmacist; protocol; venous thromboembolism

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Introduction

It is estimated that the annual incidence of venous thromboembolism (VTE) is 0.07–0.14 per 10,000 healthy children and 5.3 per 10,000 pediatric hospital admissions.[1] Enoxaparin is a low-molecular-weight-heparin that is indicated for the prophylaxis and treatment of venous thromboembolism in pediatric patients. The use of enoxaparin has increased, replacing unfractionated heparin as a more common choice for parenteral anticoagulation. Enoxaparin boasts a longer half-life, elevated subcutaneous bioavailability, and a reduced risk of heparin-induced thrombocytopenia in contrast to unfractionated heparin.[2]

The 2012 American College of CHEST Physicians guideline recommends dosing enoxaparin based on pediatric patients' weight and age.[3] Compared with adults, pediatric patients exhibit a larger volume of distribution and more rapid clearance of low-molecular-weight-heparin, accompanied by decreased plasma concentrations of antithrombin. These differences can lead to escalated dose requirements. Consequently, anti-Xa concentrations are recommended to be drawn to monitor for optimal anticoagulation in the pediatric population.[2] The CHEST guideline recommends using a target range of 0.5–1 IU/mL for anti-Xa monitoring in patients receiving therapeutic low-molecular-weight-heparin. The goal anti-Xa concentration for prophylaxis with enoxaparin is less defined, but the range of 0.1–0.3 IU/mL is cited from its use in the literature.[3]

With the role of pharmacists in the clinical care setting progressively expanding, a 2023 survey involving critical care pharmacists in adult hospitals in the United States revealed that 41% of institutions had adopted pharmacist-driven protocols for dose adjustments of

enoxaparin.[4] This practice is also extending to pediatric hospitals, where pharmacists are involved in enoxaparin dosing and monitoring. Currently, a significant portion of the literature surrounding pharmacist-to-dose (PTD) protocols for enoxaparin focuses on the efficacy of these protocols. The additional monitoring and dose adjustments that are required in the pediatric population are clinical contributions that pharmacists can make through PTD protocols; however, the literature on the impact that pharmacists have on clinical outcomes through PTD protocols remains limited.[5–6]

In 2019, West Virginia University Medicine Children's Hospital implemented a PTD protocol for enoxaparin dosing. This protocol empowered pharmacists to dose enoxaparin upon initiation, order anti-Xa plasma concentrations, and adjust dosages in accordance with a set guideline. While this guideline had existed before the implementation of the PTD protocol, its administration was predominantly overseen by physicians, with pharmacists providing recommendations as needed. Prior data collected at the institution focused on the efficacy of this guideline. This study aims to continue the investigation in this space by focusing on the impact of pharmacists, assessing rates of achieving goal anti-Xa concentrations before and after the implementation of a PTD protocol in pediatric patients.

Materials and Methods

Study Design. This retrospective, single-center chart review was conducted at West Virginia University Medicine Children's Hospital. The electronic medical record was queried for patients aged 18 years and younger who received enoxaparin while inpatient from January 2016 to September 2023. Patients were included if they had at least 1 anti-Xa concentration drawn. Patients were excluded if they met any of the following criteria: no PTD order after implementation, known coagulation disorder, estimated glomerular filtration rate (eGFR) < 10 mL/min/1.73m^2, continuation of enoxaparin from home or outside facility, received a maximum prophylactic dose of enoxaparin (30 mg every 12 hours or 40 mg every 24 hours) and did not require monitoring, or received less than 2 doses of enoxaparin (see the definitions section for additional details). Each anti-Xa concentration was considered an individual data point for analysis. Anti-Xa concentrations that were collected outside the timeframe of 4–6 hours (±30 minutes) postdose were excluded. A 30-minute buffer was allotted to account for nursing workflow. Anti-Xa concentrations drawn from January 1, 2016, to October 31, 2019, were assigned to the pre-PTD group, while concentrations drawn from January 2, 2020, to September 30, 2023, were assigned to the post-PTD group. Anti-Xa concentrations drawn from November 1, 2019, to January 1, 2020, were also excluded from the analysis to allow for a washout period before and after the implementation of the PTD protocol. Chromogenic anti-Xa assays on ACL TOP were used to measure concentrations.

Data collection. Data collection of patient demographics included age, sex assigned at birth, weight, body mass index, and eGFR. Indication, dosing, and timing of enoxaparin administration were collected. Appropriateness of the time of anti-Xa concentration collection was assessed. Anti-Xa concentrations were then categorized as being subtherapeutic, therapeutic, or supratherapeutic based on our institution-specific guideline. Finally, dose adjustments were recorded, including any notable discrepancies from the guideline.

Outcomes. The primary outcome was the rate of anti-Xa concentrations in the goal range before and after implementing a pharmacist-led enoxaparin-dosing protocol. Secondary outcomes included the number of anti-Xa concentrations drawn, the number of dose adjustments, the rate of accurately drawn anti-Xa concentrations, the rate of following the initial dose according to the guidelines, and the time to achieve the goal anti-Xa concentration before and after implementing a pharmacist-led enoxaparin-dosing protocol.

Definitions. The goal prophylaxis anti-Xa concentration was defined as 0.1–0.3 ± 0.02 IU/mL, and the goal treatment anti-Xa concentration was defined as 0.5–1 ± 0.05 IU/mL. Any other patient-specific treatment concentrations determined by the treatment team were granted ±0.05 IU/mL to account for laboratory variation. Premature neonates were defined as children 1 month of age or younger who were born before 37 weeks gestation. Coagulation disorders were defined as any disorder mentioned in the patient's history and physical that affects the blood's ability to clot and include, but are not limited to, hemophilia, Von Willebrand disease, and other clotting factor deficiencies. eGFR was calculated by the 2009 bedside Schwartz equation.

Statistical Analysis. Each laboratory concentration drawn was included individually for statistical analysis. After implementing the PTD protocol, an estimated 79% of concentrations were found to be in goal based on previous data collected at our institution. For the sample size calculation, a difference of 15% was considered statistically significant. A sample size of 300 anti-Xa concentrations (150 anti-Xa concentrations pre-PTD and 150 anti-Xa concentrations post-PTD) was required to meet a power of 80%. Alpha was set at 0.05. The data were analyzed using a X^2 analysis.

Results

A total of 106 patients were included, with 55 patients in the pre-PTD group and 51 in the post-PTD group. Patients in both groups had similar characteristics in terms of weight, body mass index, eGFR, and age (Table 1). There were more patients in the

Table 1. Characteristics of Patients Who Received Enoxaparin

	Pre-PTD (n = 55)	Post-PTD (n = 51)	p value
Weight, mean ± SD, kg	51.6 ± 37.1	51.6 ± 37.6	0.99
BMI, mean ± SD, kg/m^2	26.5 ± 9.0	24.7 ± 10.2	0.37
eGFR, mean ± SD, mL/min/1.73m^2	86.2 ± 26.2	92.7 ± 25.3	0.18
Age, mean ± SD, yr	10.8 ± 6.8	10.5 ± 6.1	0.82

PTD, pharmacist-to-dose; BMI, body mass index; eGFR, estimated glomerular filtration rate

Table 2. Patient Age Groups by Indication for Enoxaparin

	Pre-PTD (n = 55)	Post-PTD (n = 51)	p value
Prophylaxis, n (%)	23 (42)	24 (47)	0.59
0–1 mo, n (%)	1 (4)	0	0.99
≥2 mo–18 yr, n (%)	22 (96)	24 (100)	0.46
Treatment, n (%)	32 (58)	27 (53)	0.59
Premature neonate, n (%)	3 (9)	0	0.24
1–2 months, n (%)	3 (9)	1 (4)	0.62
3 mo–1 yr, n (%)	4 (13)	4 (8)	0.99
2–4 yr, n (%)	0	8 (16)	0.002
5–18 yr, n (%)	22 (69)	14 (27)	0.17

PTD, pharmacist-to-dose

pre-PTD treatment group aged 5–18 years (p = 0.17), while there were more patients in the post-PTD treatment group aged 2–4 years (p = 0.002). There were 3 (9%) premature neonates included in the pre-PTD group compared with none in the post-PTD group (p = 0.24) (Table 2).

In the pre-PTD group, 233 concentrations were drawn. Of those, 200 (85.8%) were drawn appropriately, and 140 (70%) were in the goal range. In the post-PTD group, 227 concentrations were drawn. Of those, 200 (88.1%) were drawn appropriately, and 140 (70%) were in the goal range (Table 3).

The rate of appropriateness of the first dose of enoxaparin was similar across both groups. There was a total of 12 instances, 4 in the pre-PTD group and 8 in the post-PTD group, where first doses were rounded to the nearest available syringe size for administration. This rounding caused doses to lie beyond 10% of the dose recommended by the guideline. Of the 12 other instances where initial doses fell outside of the guideline, 5 were recommendations from the hematology/oncology team. The time to reach the goal anti-Xa concentration was 2.25 days in the pre-PTD group compared with 1.02 days in the post-PTD group. There was no statistical difference in the number of dose adjustments between the 2 groups (Table 4). A higher number of dose adjustments occurred in the pre-PTD group due to the provider choice compared with the post-PTD group (13 versus 4, respectively). Additional dose adjustments in the post-PTD group were based on changes in clinical status in patients who were receiving prophylaxis dosing and transitioned to treatment dosing (n = 2) and dose adjustments for ease of administration, either during the inpatient admission or for outpatient use (n = 2) (Table 5).

Discussion

There was no difference in the rate of anti-Xa concentrations in the goal range before and after implementing a pharmacist-led enoxaparin dosing protocol. The same dosing guideline for initiating and adjusting enoxaparin dosing based on concentrations was used both before and after implementing the PTD protocol. Using the same institutional dosing guideline may have contributed to the similar rates of anti-Xa concentrations that were in goal. In the post-PTD group, there were fewer provider-driven dose adjustments (8% vs 21.3%; p = 0.03). There also were more concentrations that were drawn appropriately (88.1 vs 85.8%; p = 0.47), although this was not statistically significant. This highlights the crucial role pharmacists can play in managing anticoagulation in pediatric patients through effective monitoring and dose adjustments.

Table 3. Anti-Xa Concentrations

	Pre-PTD Concentrations	Post-PTD Concentrations	p value
Total concentrations drawn, n	233	227	
Concentrations drawn after dose adjustments, n (%)	63 (27)	48 (21)	0.14
Concentrations drawn appropriately, n (%)	200 (86)	200 (88)	0.47
Concentrations drawn appropriately, not in goal, n (%)	60 (30)	60 (30)	0.87
Concentrations drawn appropriately, in goal, n (%)	140 (70)	140 (70)	0.73

PTD, pharmacist-to-dose

Table 4. Evaluation of Initial Dosing of Enoxaparin

	Pre-PTD	Post-PTD	p value
First dose appropriate, n (%)	43 (78)	39 (76)	0.84
First dose not appropriate: rounding, n (%)	4 (7)	8 (16)	0.17
First dose not appropriate: other, n (%)	8 (15)	4 (8)	0.28
Time to goal anti-Xa in days, mean ± SD	2.25 ± 5.21	1.02 ± 0.69	0.12
Number of dose adjustments, n (%)	63 (32)	48 (24)	0.14

PTD, pharmacist-to-dose

Table 5. Reasons for Dose Adjustments of Enoxaparin

	Pre-PTD Dose Adjustments (63)	Post-PTD Dose Adjustments (48)	p value
Provider choice, n (%)	13 (21)	4 (8)	0.03
Protocol guidance, n (%)	46 (73)	40 (83)	0.56
Change in clinical status, n (%)	0	2 (4)	0.15
Other, n (%)	4 (6)	2 (4)	0.43

PTD, pharmacist-to-dose

All patients followed the previously defined goal range except for 1 patient who spanned both groups. This patient required an increase in the therapeutic anti-Xa range due to the continued development of clots while targeting the conventional 0.5–1 IU/mL range.

Although the difference in time to goal was not statistically significant between the 2 groups, it suggests the value that pharmacists may bring in achieving anti-Xa goal concentrations sooner. Patients in the post-PTD group achieved therapeutic anti-Xa concentrations 1.23 days earlier, which could potentially be a clinically significant difference. This difference in time to goal may have been influenced by 2 patients in the pre-PTD group with a longer time to goal (33.36 and 15.17 days). Although these patients were outside of the defined goal range, they remained clinically stable, and the medical team decided to maintain the same enoxaparin dose. It required additional concentrations to be drawn within the goal range of 0.5–1 ± 0.05 IU/mL, as defined in the Methods section, for these patients to achieve their goal.

The existing literature on enoxaparin dosing in pediatric patients primarily focuses on investigating the safety and efficacy of various dosing strategies, as well as subsequent monitoring protocols.[5–8] Wiltrout et al[5] investigated the implementation of a pharmacist-driven protocol with initial doses of therapeutic enoxaparin differing from our institution (1.5 mg/kg/dose for infants < 2 months of age and 1 mg/kg per dose for children ≥ 2 months). The same dose adjustment guidance was used. Their findings revealed that 56% of patients achieved initial anti-Xa values within the goal range, and thrombus resolution was associated with achieving anti-Xa concentrations within the therapeutic goal range. Fung et al[6] conducted a retrospective chart review of a freestanding children's hospital to determine enoxaparin dosage requirements across various age groups and concluded that the existing dosing schemes in place were inadequate to achieve the initial goal anti-Xa concentrations. Similarly, Bennett et al[9] investigated the clinical outcomes of pediatric patients who received prophylactic enoxaparin using a pharmacist-led protocol, noting lower instances of VTE in patients who achieved the goal range of 0.2–0.5 IU/mL. Although the guidance differed slightly from our institution in both initial dosing and monitoring, this literature highlights the importance of promptly and consistently obtaining prophylactic or therapeutic anti-Xa concentrations. These studies used pharmacist-led protocols; however, none compared the crucial role that pharmacists play in directing dose adjustments to achieve target anti-Xa concentrations efficiently by analyzing data before and after the implementation of these protocols. The results of this study show that pharmacist-led protocols yield similar rates of achieving goal anti-Xa concentrations while potentially reducing the time required for patients to reach these concentrations compared with the same protocols led by physicians. Although the length of stay was not assessed by this study, reducing the time to goal may result in shorter admissions.

Limitations of this research project include its retrospective nature and single-center design. The frequency and significance of bleeding and thrombotic events were not evaluated. The reliance on a patient's history

and physical to identify coagulation disorders may be a limitation if these disorders are not appropriately documented. Patients in the pre-PTD group that were included spanned approximately 33 months, and the same number of concentrations obtained in the post-PTD group was achieved in approximately 18 months. This discrepancy was not due to an increased frequency of monitoring, as the number of patients was similar in both groups; however, it may have stemmed from increased usage of enoxaparin. Physicians and pharmacists may have become more comfortable with dose adjustments as the use of enoxaparin in pediatrics has increased in recent years, and nursing staff may have become more familiar with obtaining the correct concentrations. It is challenging to determine the extent to which the increased frequency of enoxaparin use would have impacted the results of this study. However, the rising need for monitoring accompanying the prescribing of enoxaparin presents more opportunities for pharmacists to be involved in clinical care.

Conclusion

There was no difference in the rate of anti-Xa concentrations that were in the goal range before and after the implementation of a pharmacist-led enoxaparin dosing protocol. This likely stemmed from the use of the same dosing guideline among both groups. PTD protocols will enable physicians to focus on other aspects of clinical care while pharmacists oversee the dosing and monitoring of enoxaparin to achieve optimal anticoagulation and positive outcomes. These findings indicate that PTD protocols can and should be implemented.

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Ethical Approval and Informed Consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and have been approved by the appropriate committees at our institution.

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