A Critical Evaluation of Enoxaparin Dose Adjustment Guidelines in Children

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OBJECTIVES The purposes of this study are to perform a large-scale evaluation of the standardized dosage adjustment nomogram recommended by the American College of Chest Physicians (CHEST) for the management of enoxaparin in hospitalized pediatric patients and to determine the necessity of routine and repeated anti-factor Xa (anti-Xa) levels.

METHODS A retrospective cohort study was designed, and charts were reviewed in a single tertiary care institution for all patients who received enoxaparin between October 1, 2010, through September 30, 2016. Patients were included if they were receiving treatment doses of enoxaparin according to the pediatric CHEST guidelines, had a subtherapeutic or supratherapeutic anti-Xa level drawn at 3.5 to 6 hours after a dose, had a dose changed in an attempt to attain a therapeutic anti-Xa level, and had a second anti-Xa level drawn 3.5 to 6 hours after the dose change. Descriptive statistical methods were used to characterize the ability of dose adjustment via a nomogram to attain an anti-Xa of 0.5 to 1 unit/mL.

RESULTS A total of 467 patients were identified who received the appropriate initial dose and dosage adjustment and whose levels were drawn according to the CHEST guidelines. In patients who had an initial anti-Xa level of <0.35 units/mL and received the nomogram recommended dose increase of $25\% \pm 5\%$, 28 out of 96 patients (29.2%) reached therapeutic levels. Of 197 patients who had an initial anti-Xa level between 0.35 and 0.49 units/mL and who received the nomogram recommended dose increase of $10\% \pm 5\%$, 116 (58.9%) reached therapeutic levels. Of 50 patients with an initial anti-Xa level between 1.1 and 1.5 units/mL and who received the nomogram dose decrease of $20\% \pm 5\%$, 31 (62%) reached therapeutic levels.

CONCLUSIONS The current dosage adjustment nomogram recommended by the CHEST guidelines does not reliably lead to therapeutic anti-Xa levels when used to adjust enoxaparin doses in pediatric patients.

ABBREVIATIONS anti-Xa, anti-factor Xa; CHEST, American College of Chest Physicians; LMWH, low-molecular weight heparin; UFH, unfractionated heparin

KEYWORDS anti-factor Xa; children; enoxaparin; factor Xa; guidelines; nomogram; pediatric; pharmacokinetics

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Introduction

With advances in pediatric care, more children are admitted to critical care units, undergo central venous catheterization, and experience invasive procedures, increasing the risk for venous thromboembolism.^{1–4} Thrombosis in children is frequently treated with unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and vitamin K antagonists.^{1,5} Treatment with LMWHs holds advantages of predictability, stable pharmacokinetics, absence of dietary or drug interactions, and decreased need for monitoring as compared with UFH and vitamin K antagonists.⁶ Low-molecular weight heparins also have longer half-lives than does UFH, allowing for once- or twice-daily subcutaneous administration.⁵

Enoxaparin is a commonly used LMWH in pediatric patients. The American College of Chest Physicians

(CHEST) Evidence-Based Clinical Practice Guidelines include guidelines and nomograms regarding the dosing, monitoring, and adjustments of enoxaparin in pediatric patients.^{5,7} The CHEST guidelines suggest an initial treatment dose of 1.5 mg/kg/dose for patients aged less than 2 months and a 1 mg/kg/dose for patients aged greater than 2 months, the dose to be administered subcutaneously every 12 hours to target anti-factor Xa (anti-Xa) levels between 0.5 and 1.0 units/mL from a blood sample taken 4 to 6 hours following a subcutaneous injection.⁵ As a result of predictable kinetics, monitoring of anti-Xa levels in adult patients treated with enoxaparin is not routinely recommended.⁸ However, achievement of desired therapeutic anti-Xa levels in pediatric patients after initiating enoxaparin therapy appears to be less predictable than in adults when using weight-based dosing.^{9,10} Factors possibly affecting

Table 1. Pediatric Dosage Adjustment Nomogram

Anti-Xa Result (units/mL)	Dose Titration
<0.35	Increase dose by 25%
0.35–0.49	Increase dose by 10%
0.5–1	No change in dosage
1.1–1.5	Decrease dose by 20%
1.6–2	Hold dose for 3 hr and decrease dose by 30%

anti-Xa, anti-factor Xa

pharmacokinetics in pediatric patients include kidney function, altered plasma binding, age, and weight, all of which may result in varying dose requirements.^{11–13} Therefore, a dosage adjustment nomogram in the CHEST guidelines recommends titrating the enoxaparin dose for pediatric patients who are not within the therapeutic range following an initial anti-Xa level (Table 1).⁷

The dosage adjustment nomogram recommended by the CHEST guidelines was validated in 1997 with 12 patients and used reviparin as the LMWH.¹⁴ A larger-scale evaluation of the nomogram has not been performed. The need to review the current nomogram was prompted by several factors. Several recent pharmacokinetic and clinical studies^{1,15–18} have reported considerable variation in the initial milligram per kilogram dose of enoxaparin recommended between neonatal and pediatric patients to achieve a therapeutic anti-Xa level. However, other factors must also be considered to improve enoxaparin management in pediatric patients. A study by Andrade-Campos et al¹⁸ reported a mean of 3 dose changes and 11 days to reach target anti-Xa levels in pediatric patients receiving enoxaparin. Similarly, in a study by Ho et al,¹⁵ the number of dosage adjustments required per patient ranged from 1 to 11, suggesting the necessity of routine anti-Xa monitoring. However, there is often difficulty with intravenous access and patient tolerance of obtaining repeated blood samples. In addition, there are costs associated with each assay. If the nomogram performs well, the need for additional anti-Xa monitoring after a dose change would be unnecessary.

The primary aims of this study were to perform a large-scale, institutional evaluation of the standardized dosage adjustment nomogram recommended by the CHEST guidelines for management of enoxaparin in hospitalized pediatric patients and to determine the necessity of routine initial and post-dose adjustment anti-Xa levels. This study also attempted to identify trends in age, weight, and serum creatinine that may affect attainment of therapeutic anti-Xa levels.

Materials and Methods

Institutional review board approval was obtained, and a retrospective cohort study was designed. Patients who were initiated on enoxaparin for treatment

of thrombosis while admitted to our institution were queried from the hospital electronic medical record from October 1, 2010, through September 30, 2016 (the current limits of the electronic medical record). Patients were included if they met each of the following criteria: a) received an initial enoxaparin dose, in accordance with the CHEST guidelines, of 1.5 mg/kg/dose $\pm$ 20% (for patients <2 months of age) or 1 mg/kg/dose $\pm$ 20% (for patients aged 2 months to 19 years) every 12 hours subcutaneously; b) had an anti-Xa level drawn 3.5 to 6 hours after at least the second dose; c) had a first anti-Xa level that was not within the range of 0.5 to 1 units/mL; d) had an enoxaparin dose that was subsequently changed to target a goal anti-Xa level of 0.5 to 1 unit/mL at 3.5 to 6 hours postdose; and f) had a second anti-Xa drawn 3.5 to 6 hours postdose after dose adjustment.

Data were collected for doses within 20% of the recommended initial dose and within 5% of the nomogram-recommended adjustment to account for dose rounding. Data were collected for levels drawn between 3.5 and 6 hours postdose to be pragmatic with clinical practice. If patients had multiple anti-Xa levels drawn during their inpatient stay, only the initial level and the first subsequent level after a dose adjustment were included. Patients were excluded if their creatinine clearance was calculated to be less than 30 mL/min, if they were receiving renal replacement therapy, or if mechanical circulatory support was required due to altered enoxaparin clearance.

Data collection consisted of patient sex, age, weight, height, and serum creatinine during enoxaparin therapy. Enoxaparin dose, administration times, anti-Xa levels, and sampling time were also collected.

Patient demographic data were summarized using descriptive statistical methods (mean, standard deviation, and percent). The reference ranges for serum creatinine are based on published literature¹⁹ and correlated with institutional assays and local clinical laboratory data. Enoxaparin doses were calculated in mg/kg/dose, and estimated creatinine clearance was calculated according to the modified Schwartz equation.²⁰ The percent change in enoxaparin dose and absolute and percentage change in anti-Xa levels after enoxaparin dose change were reported.

Patients were categorized into 2 groups: those that achieved therapeutic (0.5–1 units/mL) anti-Xa levels

Table 2. Patient Baseline Demographics

	Subtherapeutic Patients (n = 375)	Supratherapeutic Patients (n = 92)
Sex, male, n (%)	204 (54.4)	48 (52.2)
Age, yr, mean $\pm$ SD	4.3 $\pm$ 5.5	8.3 $\pm$ 7.4
Height, cm, mean $\pm$ SD	90.2 $\pm$ 9.6	113 $\pm$ 46.5
Weight, kg, mean $\pm$ SD	17.8 $\pm$ 20	37.9 $\pm$ 32.3
Serum creatinine, mg/dL, mean $\pm$ SD	0.34 $\pm$ 0.16	0.47 $\pm$ 0.19

after a dose change and those who still had non-therapeutic (subtherapeutic or supratherapeutic) anti-Xa levels after a dose change. Patient demographic variables and dose changes were compared between the 2 groups.

Statistical analysis was performed with Excel 2013 (Microsoft, Redmond, WA) and Stata IC v.12 (StataCorp, College Station, TX). A *p* value of <0.05 was considered statistically significant *a priori*.

Results

Our query identified 1455 patients initiated on enoxaparin for treatment of thrombosis while admitted to our institution during the study period and found 898 patients with an initially non-therapeutic anti-Xa level. Within the 898 non-therapeutic patients, 467 patients met study criteria and had an initial anti-Xa level that was either subtherapeutic (n = 375) or supratherapeutic (n = 92) after enoxaparin initiation (Table 2). Enoxaparin doses were adjusted according to the CHEST guideline nomogram in 343 patients (73.4%). Therapeutic anti-Xa levels between 0.5 and 1 units/mL were attained in 175 patients (51%) after a dose adjustment. Patients were further broken down into subgroups based on initial subtherapeutic or supratherapeutic anti-Xa levels and percent dose change (Table 3).

Subtherapeutic Anti-Xa. A total of 375 patients exhibited an initial anti-Xa level that was subtherapeutic (Table 3). In this group, initial mean anti-Xa level was

0.36 units/mL and was obtained a mean of 4.2 hours after the second enoxaparin dose. For all patients, the mean dose increase was 14.9%, resulting in a mean anti-Xa level of 0.51 units/mL obtained a mean of 4.2 hours after the dose change. After the dose increase, 180 patients (48%) attained therapeutic anti-Xa levels (mean 0.64 units/mL). Four patients (1%) became supratherapeutic, and 191 patients (51%) remained subtherapeutic. Patients were then divided into groups by initial anti-Xa level (<0.35 units/mL and 0.35–0.49 units/mL) and percent dose change.

One hundred and forty-five patients were found to have an initial anti-Xa level of <0.35 units/mL. Although the nomogram calls for a dose increase of 25%, the mean dose change in this study was 20.9%. This resulted in 45 patients (31%) attaining therapeutic anti-Xa levels. Of the 145 patients with an anti-Xa of <0.35 units/mL, 96 patients (66.2%) had the nomogram-recommended dose increase of 25% $\pm$ 5% and 28 patients (29.2%) attained therapeutic anti-Xa levels (Table 3). No patients were supratherapeutic, and 68 patients (70.8%) remained subtherapeutic.

Similarly, 230 patients had an initial anti-Xa level between 0.35 and 0.49 units/mL. For patients with this initial anti-Xa level, the nomogram calls for a dose increase of 10%. In this study, the mean dose change was 11.2%, which resulted in 135 patients (58.7%) attaining a therapeutic anti-Xa level. Of the 230 patients with an anti-Xa level between 0.35 and 0.49 units/mL, 197 patients (85.6%) had the nomogram-recommended

Table 3. Summary of Dose Changes and Anti-Xa Level Response

	Dose Change (%; mean $\pm$ SD)	Anti-Xa Response (%; mean $\pm$ SD)	Therapeutic, n (%)
Initial subtherapeutic (<0.5 units/mL) (n = 375)	14.9 $\pm$ 6.8	48.6 $\pm$ 63.6	180 (48)
Initial concentration < 0.35 (n = 145)	20.9 $\pm$ 5.5	76.1 $\pm$ 77.0	45 (31)
Dose increased 25% $\pm$ 5% (n = 96)	20.9 $\pm$ 1.6	69.0 $\pm$ 69.4	28 (29.2)
Initial concentration 0.35–0.49 (n = 230)	11.2 $\pm$ 4.6	31.2 $\pm$ 45.6	135 (58.7)
Dose increased 10% $\pm$ 5% (n = 197)	9.9 $\pm$ 2.2	30.6 $\pm$ 43.9	116 (58.9)
Initial supratherapeutic (>1 units/mL) (n = 92)	–23.1 $\pm$ 11.3	–31.9 $\pm$ 21.5	57 (63)
Initial concentration 1.1–1.5 (n = 88)	–22.5 $\pm$ 10.9	–22.3 $\pm$ 21.5	55 (62.5)
Dose decreased 20% $\pm$ 5% (n = 50)	–23.5 $\pm$ 2.5	–23.5 $\pm$ 24.5	31 (62)
Initial concentration 1.6–2 (n = 4)	–36.2 $\pm$ 13.4	–29.7 $\pm$ 20.2	2 (50)
Dose held and decreased 30% $\pm$ 5% (n = 0)	0	0	0

anti-Xa, anti-factor Xa

Table 4. Comparison of Demographics in Patients Who Received Nomogram-Compliant Dosage Adjustments

	Postadjustment Therapeutic	Postadjustment Non-therapeutic	p value
Subtherapeutic (n = 293)	n = 144	n = 149	
Sex, male, n (%)	85 (59)	81 (54.4)	0.42
Age, yr	6.4 ± 6.3	2.93 ± 4.3	<0.001
Weight, kg, mean ± SD	24 ± 21.2	13.4 ± 16.5	<0.001
Height, cm, mean ± SD	105 ± 42.9	80 ± 30.9	<0.001
Serum creatinine, mg/dL, mean ± SD	0.37 ± 0.20	0.30 ± 0.13	0.004
Suprathreshold (n = 50)	n = 31	n = 19	
Sex, male, n (%)	18 (58)	11 (57.9)	0.99
Age, yr	6.3 ± 6.8	7.5 ± 7.9	0.57
Weight, kg, mean ± SD	31.9 ± 32.4	32.7 ± 30.9	0.93
Height, cm, mean ± SD	102 ± 47.1	107.6 ± 49.1	0.69
Serum creatinine, mg/dL, mean ± SD	0.43 ± 0.19	0.46 ± 0.23	0.62

dose increase of 10% ± 5%, and 116 patients (58.9%) attained therapeutic anti-Xa levels (Table 3). Two patients (<1%) became suprathreshold, and 79 patients (40.1%) remained subtherapeutic.

Suprathreshold Anti-Xa levels. A total of 92 patients exhibited an initially suprathreshold anti-Xa level (Table 3). The initial mean anti-Xa level was 1.2 units/mL and was obtained a mean of 4.1 hours after the second enoxaparin dose. For all patients, the mean dose change was -23.1%, resulting in a mean anti-Xa level of 0.93 units/mL obtained a mean of 4.1 hours after the dose change in all patients. After the dose decrease, 57 patients (63%) had a therapeutic anti-Xa level (mean 0.80 units/mL). Three patients (3.3%) became subtherapeutic and 32 patients (34.8%) remained suprathreshold. Patients were then divided into groups by initial anti-Xa level (1.1–1.5 units/mL and 1.6–2 units/mL) and percent dose change.

In total, 88 patients were found to have an initial anti-Xa level between 1.1 and 1.5 units/mL. In these patients, the nomogram calls for a dose decrease of 20%. The mean dose change was -22.5% in this study, which resulted in 55 patients (62.5%) obtaining therapeutic anti-Xa levels. When patients had doses adjusted according to the recommended dose decrease in the nomogram of 20% ± 5%, 31 out of 50 patients (62%) attained therapeutic anti-Xa levels (Table 3). Sixteen patients (32%) remained suprathreshold, and 3 patients (6%) became subtherapeutic.

Four patients had an initial anti-Xa level between 1.6 and 2 units/mL. After a mean dose change of -36.2%, 2 patients (50%) attained a therapeutic anti-Xa level, whereas 2 patients (50%) remained suprathreshold. No patients had enoxaparin doses adjusted in strict accordance with the nomogram-recommended 30% decrease.

All patients who received the appropriate adjustments according to the nomogram were further categorized

by sex, age, weight, height, and serum creatinine. A significant difference was identified in subtherapeutic patients for age, weight, and height (p values < 0.001) when comparing patients with therapeutic versus non-therapeutic postadjustment anti-Xa levels (Table 4). A scatter plot of percent changes in enoxaparin dose versus percent change in anti-Xa was developed, and no trends were identified (Figure).

Discussion

This is the first large-scale, critical evaluation of the nationally standardized dosage adjustment nomogram recommended by the CHEST guidelines for management of enoxaparin in pediatric patients. We have demonstrated that the attainment of therapeutic levels after a dose adjustment according to the published CHEST nomogram is low. This should lead clinicians who are aiming for therapeutic levels to monitor levels after dose changes and not merely assume that adjustment will result in therapeutic levels. The lack of consistent attainment of therapeutic anti-Xa levels when using the current nomogram also suggests that other strategies for dose adjustment should be investigated.

An increase in dose to attain a therapeutic level was less likely to succeed than was decreasing a dose. When patient demographics were evaluated in this regard, patients with initial subtherapeutic concentrations were younger and smaller in size than patients with suprathreshold concentrations (Table 4). It has been well recognized^{11,15–17} that infants and neonates require larger doses than do older and larger patients. Our data would suggest that dose adjustment guidelines should also take into account age of the patient in order to attain therapeutic anti-factor Xa levels in an efficient manner, especially among patients found to be subtherapeutic. In addition, body habitus/weight should be considered, as we have previously reported²¹ that

Figure. Relationship between change in enoxaparin dose and anti-factor Xa level.

obese patients typically require lower doses of enoxaparin. Although we cannot conclusively recommend that dose adjustments should take into account if a patient is obese, we would suggest caution in making enoxaparin dose adjustments according to the currently published nomogram in this particular patient population. An optimal methodology for dose adjustment appears to require incorporation of additional patient variables rather than simple percent changes in dose based upon prior anti-factor Xa levels.

The use of population pharmacokinetic models may be a method for improving dose adjustment in pediatric patients receiving enoxaparin.²² We have recently published²³ a model developed in pediatric patients describing enoxaparin pharmacokinetic disposition, which incorporates body size, kidney function, and other physiologic variables. In younger patients, the use of postmenstrual age may improve dosing.²⁴

It is notable from our data that the change in anti-factor Xa levels was not linear, despite the dosing nomogram suggesting percentage changes in dose (Figure). In patients who had a dose adjustment of 20%, the change in anti-Xa ranged from -60% to 340%, showing a lack of correlation between the dose change and change in anti-Xa level. Model-guided precision dosing would be useful in this scenario to incorporate patient-specific physiologic parameters with dosing that does not appear to exhibit a simple linear relationship with anti-factor Xa levels.

Because it is well recognized that there is alternative dosing for enoxaparin outside of that recommended by the CHEST guidelines, dose variations should be considered in the limitations of this study. In patients

with an initial anti-Xa level of <0.35 units/mL, not attaining therapeutic levels may be due to a low initial dose, even following a dosage adjustment per the nomogram, and represents a limitation for this study population. Other limitations associated with this study are those germane to retrospective reviews. This study was not designed to establish dose initiation strategies for enoxaparin or to assess clinically therapeutic anticoagulation outcomes or adverse events. For supratherapeutic patients, data were not collected for the level prior to the second dose as recommended by the CHEST guidelines. The utility of blood sampling and attaining therapeutic anti-Xa levels should be evaluated in the context of a patient's clinical situation. Future directions for evaluation of dosing adjustment include incorporation of disease state and other patient-specific parameters.

Conclusions

Adjustment of enoxaparin doses by the nationally standardized nomogram recommended by the CHEST guidelines does not reliably result in therapeutic anti-Xa levels. Alternative methods for enoxaparin dose adjustment should be investigated.

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