Enoxaparin Dosing Requirements and Anti-Xa Monitoring in Specialty Patient Populations: A Case Series of Pediatric; Renal-Impaired; Extremes of Body Weight; and Pregnant Patients

Mousavi K, Klejmont L, Desai S and Ahuja T*  
1 Department of Pharmacy, CHI Baylor-St. Luke’s Medical Center, Houston, USA  
2 Department of Pharmacy, Maria Fareri Children’s Hospital, Westchester Medical Center, NY, USA  
3 Department of Pharmacy, Children’s Medical Center, Dallas, USA  
4 Department of Pharmacy, New York University Langone Medical Center, NY, USA

Abstract

The use of enoxaparin in specialty populations has been excluded from clinical trials, including those with renal dysfunction, extremeness of body weight, pregnant patients, and pediatric patients. Much of the data of enoxaparin in these patients is derived from pharmacokinetics. Monitoring anti-factor Xa activity (Anti-Xa) to measure the anticoagulant effects may be of benefit. This retrospective review was conducted to evaluate if specialty patient populations admitted to a hospital setting had a peak Anti-Xa measured to guide in optimal enoxaparin dosing. A case series of patients admitted to New York University Langone Medical Center (NYULMC) between December 2012 and July 2014 who received at least three consecutive doses of enoxaparin for the treatment of VTE and had a peak Anti-Xa 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) ≤30 ml/min at time of initiation of enoxaparin, body weight ≤50 kg or ≥120 kg. A total of 31 patients were included in the analysis. The percentage of patients that achieved a therapeutic Anti-Xa 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 Anti-Xa level drawn was greatest for the obese patients (100%) followed by pregnancy (67%), low body weight (57%), renal impaired (33-40%), and lastly pediatrics (9%). Additionally, neonates and young children required increased enoxaparin dosing to achieve therapeutic Anti-Xa. Optimal dosing of enoxaparin in specialty patient populations has not been established. Surrogate laboratory monitoring of peak Anti-Xa levels may help predict the pharmacokinetics of enoxaparin. Higher initial doses of enoxaparin may be needed in pediatric patients to attain therapeutic Anti-Xa levels.

Keywords: Enoxaparin; Specialty populations; Therapeutic drug monitoring; Anti-factor Xa; Low-molecular-weight heparin

Introduction

An estimated 900,000 adults are affected by Venous Thromboembolism (VTE) in the United States annually, resulting in an estimated 60,000 to 100,000 deaths yearly [1]. After acute coronary syndrome and stroke, VTE is the third most common cardiovascular disease in the US [2]. In contrast, VTE in children is rare though the incidence is noted to be increasing with an estimated 70% increase in annual VTE from 2001 to 2007 in hospitalized children [3]. Major risk factors for VTE in adult patients include conditions such as morbid obesity, acute medical illnesses, and conditions that affect the coagulation cascade such as hormonal changes during pregnancy or the presence of central venous catheters [1,4-6]. 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 [7,8]. Paradoxically, the optimal treatment of VTE in specialty patient populations, such as pediatrics, morbid obesity, low body weight, kidney disease and pregnancy, is uncertain. In the general population, Low Molecular Weight Heparins (LMWHs), 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 Heparin Induced Thrombocytopenia (HIT). Enoxaparin, a LMWH, is indicated for treatment and prevention of VTE and acute coronary syndrome. According to the American College of Chest Physicians, LMWH is equivalent to UFH for the treatment of patients with VTE including Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) [9-11].

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]. In addition to renal dysfunction, the majority of enoxaparin studies excluded specialty patient populations such as pregnant patients and extremes of body weight. There are concerns that weight-based dosing of LMWH in obese patients may lead to overdosing and increased bleeding, and in pregnant patients there are concerns regarding the changes in maternal weight as the pregnancy progresses [13]. Additionally, although recent studies have suggested higher doses may be needed in pediatric patients to target an anti-factor Xa (Anti-Xa) between 0.5-1.0 IU/mL, enoxaparin has not been studied extensively in this population [14].

LMWHs are not subject to nonspecific binding of plasma proteins, thus, the anticoagulant effects are more predictable and typically do not require routine laboratory monitoring compared to UFH. However, monitoring Anti-Xa activity as a surrogate, in

*Corresponding author: Tania Ahuja, Department of Pharmacy, New York University Langone Medical Center, 550 First Avenue, New York, NY 10016, USA, Tel: +1 646-929-7875; E-mail: tania.ahuja@nyumc.org

Received July 06, 2017; Accepted July 18, 2017; Published July 25, 2017


Copyright: © 2017 Mousavi K, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
specialty patient populations including those with renal dysfunction, extremes of body weight and pediatrics, may be warranted to ensure that enoxaparin’s anticoagulant effect is safe and efficacious. Anti-Xa levels measure the anticoagulant effect of LMWH rather than drug concentration. Interestingly, clinical trials evaluating LMWHs did not target Anti-Xa levels to guide dosing and most of the data regarding Anti-Xa monitoring has been determined retrospectively. As part of a quality assessment, we sought to evaluate our own institutional recommendation to monitor a peak Anti-Xa level in these specialty populations to guide in optimal enoxaparin dosing.

Methods

This was a single-center, retrospective review conducted at New York University Langone Medical Center (NYULMC) between December 2012 and July 2014. Electronic health records of patients who received at least three consecutive doses of enoxaparin for the treatment of VTE and had a peak Anti-Xa level drawn at steady state were reviewed. Steady state was defined as Anti-Xa at three to 6 h 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 time of initiation of enoxaparin, body weight ≤50 kg or ≥120 kg. All other patients were excluded.

Data was obtained through a retrospective medical record review of baseline demographics, enoxaparin dosing regimens, anti-Xa measurements, incidence of Heparin-induced Thrombocytopenia (HIT), and mortality associated with recurrent thrombotic or bleeding events within two weeks of initiation of enoxaparin. CrCl was estimated using the Cockcroft-Gault equation for adults and the modified Schwartz equation for pediatrics.

Heparin Induced Thrombocytopenia (HIT) was defined as a decrease in initial platelet count of greater than or equal to 50% after initiation of enoxaparin and a positive Heparin-platelet Factor 4 (HPF4) antibody. Major bleeding was defined as one of the following: fatal bleed; decrease in hemoglobin by 2 g/dL in a 24 h period; bleed associated with transfusion of 2 or more units of whole blood, RBCs, or surgical intervention; symptomatic bleed in a critical area or organ (intracranial, pulmonary, or retroperitoneum). Minor bleeding was defined as overt bleeding associated with an intervention or discontinuation of therapy that did not meet criteria for major bleed.

The primary outcome was the percentage of patients that achieved a therapeutic Anti-Xa at the first level drawn. Therapeutic Anti-Xa 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. Secondary outcomes included the percentage of patients with Anti-Xa level that were therapeutic at day 7, the mean days it took to reach a therapeutic range, major or minor bleeding events or incidence of HIT, and progression or occurrence of thrombosis. Descriptive statistics were used to analyze the data.

Results

In total, 1552 patient encounters with enoxaparin administrations were screened (80 pediatric and 1472 adult patients). Patients were excluded if they received less than 3 enoxaparin doses (n=762), followed by prophylactic dosed enoxaparin (n=536). 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 Anti-Xa drawn, followed by Anti-Xa not 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 pediatrics, 35 years (29-39 years) for pregnancy, 84 years (80-89 years) for the renal impaired, 63 years (55-71 years) for obese and 80 years (48-89 years) for low body weight. The indication for the majority of the enoxaparin utilized in these specialty populations was venous thromboembolism including deep vein thrombosis and pulmonary embolism (Table 1). The percentage of patients who achieved a therapeutic Anti-Xa level (0.5-1.2 IU/mL for twice daily enoxaparin or 1-2 IU/mL for once daily enoxaparin) with the first Anti-Xa level drawn was greatest for the obese patients (100%) followed by pregnancy (67%), low body weight (57%), renal impaired (33-40%), and lastly pediatrics (9%). The pediatric patients’ first Anti-Xa was sub-therapeutic in the majority (82%), followed by the renal impaired, low body weight, and pregnant patients. Only 1 pediatric patient had a supratherapeutic Anti-Xa with the first level drawn (Table 2). We stratified the starting weight based dose for adults and pediatrics. For adults, the initial mean weight based dose per administration for twice daily dosing was 1.09 ± 0.16 mg/kg, well within the expected range recommended (Figure 1). Although NYULMC’s standard for dosing enoxaparin in neonates and children is 1.5 mg/kg subcutaneously every 12 h for children <2 months of age and 1 mg/kg subcutaneously every 12 h for children >2 months of age, we noted a slightly increased enoxaparin dosing requirement in neonates and young children. At our institution, pediatric patients less than 1 year of age in an ICU setting required higher doses (mean of 2.02 ± 0.65 mg/kg every 12 h for twice daily dosing) and took longer to meet therapeutic goals (mean of 4 ± 2 days), indicating that they may require a higher starting dose than other pediatric patients. Furthermore, mean weight based dosing was 1.58 ± 0.55 mg/kg for neonates and 1.4 ± 0.45 mg/kg for children >2 months of age (Figure 2).

We also aimed to evaluate the percentage of patients that achieved a therapeutic Anti-Xa at day 7 and found 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 three patients with CrCl >30 mL/min, with 1 patient therapeutic at 7 days and 2 sub therapeutic at 7 days. There were no bleeding events reported in patients with moderate or severe renal impairment.

Discussion

Our results identified that majority of specialty patient populations were treated with enoxaparin according to guideline recommendations. Although data on efficacy and safety of the use of enoxaparin in these specialty populations is mainly observational and extrapolated from pharmacokinetic studies, LMWHs are often preferred over other agents due to predictable anticoagulation effect, infrequent monitoring, and low incidence of HIT. Furthermore, although therapeutic Anti-Xa ranges have not been clinically validated, peak Anti-Xa levels, drawn 4 hrs following LMWH administration, have been recommended by a consensus of expert practitioners. Therapeutic dosed enoxaparin should achieve a peak Anti-Xa of 0.6 to 1 IU/mL for twice daily dosing and 1-2 IU/mL for once daily dosing [13]. At our institution, enoxaparin use in specialty patient populations was associated with few adverse outcomes and was found to be efficacious in most specialty patient populations. Enoxaparin use in patients with moderate to severe renal impairment (CrCl 30-50 mL/min and CrCl <30 mL/min) with Anti-Xa monitoring was infrequent at NYULMC. Additionally, the patients with impaired renal function tended to be elderly, had lower body weights, and were among the least likely to reach therapeutic goal. Dose adjustments were rarely made in both of these specialty patient populations, despite sub-therapeutic levels without an observed increase in thromboembolism. Although no adverse outcomes occurred during treatment, the results...
suggest that patients with lower body weight and renal impairment may need more frequent Anti-Xa monitoring and/or dose adjustments.

There is a risk of LMWH 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 [13]. In addition, renal insufficiency is a risk factor in of itself for bleeding with anticoagulation therapy [15]. A pharmacokinetic study of 19 patients (CrCl range 11.6-29.4 mL/min) has suggested that dose-adjusted enoxaparin (1 mg/kg every 24 h) is associated with achieving a therapeutic peak in 74% of the patients studied, with no major bleeding events noted [16]. Previous studies have suggested CrCl <30 mL/min as the threshold for enoxaparin accumulation and threshold for when to dose reduce to decrease the risk of clinically significant accumulation and bleeding [17]. The American College of Chest Physicians endorses Anti-Xa levels in patients with severe renal insufficiency to minimize bleeding risk [18]. However, there is no consensus regarding the level of renal dysfunction, below which there is risk of accumulation [19]. Some studies suggest that a CrCl of <50 mL/min may lead to accumulation of enoxaparin [20,21]. At our institution, the antithrombotic therapy

<table>
<thead>
<tr>
<th>Primary Outcome</th>
<th>Age ≤ 18 (n=11)</th>
<th>CrCI&lt;30 ml/min (n=3)</th>
<th>CrCI 30-50 ml/min (n=5)</th>
<th>ABW ≤ 50 kg (n=7)</th>
<th>ABW ≥ 120 kg (n=2)</th>
<th>Pregnant (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Xa at first level</td>
<td>Therapeutic¹</td>
<td>1 (9)</td>
<td>1 (33)</td>
<td>2 (40)</td>
<td>4 (57)</td>
<td>2 (100)</td>
</tr>
<tr>
<td></td>
<td>Sub-Therapeutic</td>
<td>9 (82)</td>
<td>2 (67)</td>
<td>3 (60)</td>
<td>4 (57)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Supra-Therapeutic</td>
<td>1 (9)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Secondary Outcomes</td>
<td>Age ≤ 18 (n=11)</td>
<td>CrCI&lt;30 ml/min (n=3)</td>
<td>CrCI 30-50 ml/min (n=5)</td>
<td>ABW ≤ 50 kg (n=7)</td>
<td>ABW ≥ 120 kg (n=2)</td>
<td>Pregnant (n=3)</td>
</tr>
<tr>
<td>Anti-Xa at first at 7 days</td>
<td>Therapeutic¹</td>
<td>9 (82)</td>
<td>1 (33)</td>
<td>3 (60)</td>
<td>4 (57)</td>
<td>2 (100)</td>
</tr>
<tr>
<td></td>
<td>Sub-Therapeutic</td>
<td>2 (18)</td>
<td>2 (67)</td>
<td>2 (40)</td>
<td>3 (43)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Supra-Therapeutic</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td># of dose adjustments to reach Therapeutic range, mean (range)</td>
<td>3 (1-5)</td>
<td>0.5 (0-1)</td>
<td>-</td>
<td>-</td>
<td>1 (0-2)</td>
<td>-</td>
</tr>
<tr>
<td>Days to reach Therapeutic range, mean (range)</td>
<td>4 (1-8)</td>
<td>7 (1-13)</td>
<td>2 (2-3)</td>
<td>2 (1-3)</td>
<td>5 (2-7)</td>
<td>3 (2-4)</td>
</tr>
<tr>
<td>Major or minor bleeding events</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Incidence of HIT</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Progression or reoccurrence of thrombosis</td>
<td>1 (9)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

¹Anti-Xa therapeutic range at our institution is between 0.5 to 1.2 for twice daily, and 1.0 to 2.0 for daily all values are represented as n (%) unless specified

Table 2: Primary and secondary outcomes.
oversight committee recommends monitoring Anti-Xa in patients with severe renal insufficiency (CrCl <30 mL/min) and to consider monitoring for peak effect in patients with moderate renal impairment (CrCl 30-50 mL/min) as well. Furthermore, the group with CrCl <50 mL/min took the longest to reach a therapeutic Anti-Xa level in our study, further demonstrating that the exact monitoring parameters and dosing have yet to be determined. Of note, we did not assess for patients being ‘bridged’ to warfarin or the concomitant INR at the time of enoxaparin administration.

In addition, although subcutaneous administration of enoxaparin results in close to 100% bioavailability, with concentrations mainly in the plasma, there is some concern that there may be bioaccumulation in obese patients as well. However, the bleeding risk in this population appears to be low [13,21,22]. At our institution, dosing recommendations for enoxaparin are standard weight-based dosing as recommended in the package insert for enoxaparin; however we do suggest considerations to monitor peak Anti-Xa in patients with weights >120 kg or BMI>35. Two patients in our cohort with body weight >120 kg achieved therapeutic Anti-Xa.

Antithrombotic therapy in the pregnancy population is often challenging due to uncertainties with changes in maternal weight and bleeding risks for both the mother and the fetus. Although the data varies with regards to dose adjustments of enoxaparin during pregnancy as maternal weight changes [23,24], our institution suggests monitoring peak Anti-Xa in pregnant patients receiving enoxaparin.

This retrospective review also highlights the need for higher initial doses in pediatric patients <1 year of age. At least one study has suggested that critically-ill, 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 h vs. 1 mg/kg every 12 h) [25,26]. Further prospective studies determining the most effective initial enoxaparin dose could significantly decrease length of stay and provide better quality care for pediatric patients.

There are several limitations to our review, including the retrospective design, small sample size, and time frame for which we were able to evaluate bleeding and thromboembolic events. We sought to review cases of patients hospitalized in specialty groups that had peak Anti-Xa levels monitored with enoxaparin use. However, our sample size was limited with many subgroups. Although Anti-Xa levels were monitored, many times the levels were not drawn at steady state, as indicated by patients we excluded from our review. In addition, despite sub-therapeutic Anti-Xa levels in our moderate and severe renal impaired population, we did not notice increased embolic events around the time of enoxaparin administration. Since we did not collect concomitant bridge therapy with warfarin, we cannot say with certainty that these doses are safe for all patients with moderate or severe renal impairment. Our case review depicts the challenges with monitoring peak Anti-Xa levels in hospitalized patients, such as timing of appropriate laboratory assessment.

Conclusion

In conclusion, optimal dosing of enoxaparin in specialty populations including those with renal dysfunction, extremes of body weight, pregnant patients and pediatrics has not been established. Surrogate laboratory monitoring of peak Anti-Xa levels may help predict the pharmacokinetics of enoxaparin. Higher initial doses of enoxaparin may be needed in pediatric patients to attain therapeutic Anti-Xa levels. To further investigate the significance of Anti-Xa monitoring, we suggest studying enoxaparin Anti-Xa monitoring in larger cohorts of specialty populations to determine the clinical significance.
References