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Monitoring Enoxaparin with Antifactor Xa Levels in Severe Renal Impairment

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Abstract

Backgrounds: While several large clinical trials have proven the efficacy and safety of treatment with enoxaparin, most of these studies excluded patients with severe renal impairment and to date no large randomized studies have been conducted that assess the safety and efficacy of the drug in this subset of patients.

Objectives: To characterize antifactor Xa peak levels as therapeutic, subtherapeutic, or supratherapeutic, in non-dialysis patients with severe renal impairment who are receiving renally adjusted therapeutic doses of enoxaparin and to assess the incidence of bleeding complications in these patients.

Methods: Retrospective cohort study in a community hospital evaluating seventy-five severe renal impairment patients (creatinine clearance [CrCl] < 30 mL/min) who received at least three renally adjusted therapeutic doses of enoxaparin and had steady-state antifactor Xa peak levels collected between April 2009 and April 2015. Institutional review board approval was obtained to collect data from patients' medical records. The primary outcome was the proportion of patients whose steady-state antifactor Xa peak levels were in the therapeutic, subtherapeutic, or supratherapeutic ranges. The secondary outcome was the incidence of major bleeding.

Results: The final analysis showed that 63% of patients (n=47) had therapeutic levels, 22% (n=17) had subtherapeutic levels, and 15% (n=11) had supratherapeutic levels. No major bleeding incidents identified in the study.

Conclusion: Based on the results of this study, monitoring antifactor Xa levels is warranted to ensure the safety and efficacy of renally adjusted doses of therapeutic enoxaparin in non-dialysis patients with severe renal impairment.

Keywords: Lovenox; Low molecular weight heparin; Enoxaparin; Renal impairment; Antifactor Xa level monitoring; Therapeutic monitoring

Introduction

Chronic kidney disease (CKD) is a major public health problem in the US whose incidence and prevalence is growing. The total number of Americans living with CKD is now estimated to be more than 20 million, that is more than 10% of the US population [1]. The pathophysiology of CKD is associated with both an increased risk of bleeding, by abnormal platelet aggregation/adhesion and prolongation of bleeding time, as well as an increased risk of thrombosis, by enhancing thrombin generation and increasing the levels of fibrinogen, von Willebrand factor, and factors VII, VIII, and XIII [2]. Additionally patients with CKD are at an increased risk for developing cardiovascular disease (CVD), and are in fact more likely to die from CVD than from kidney failure [3]. Furthermore the incidence and mortality due to CVD is 10-30 times higher in those with CKD than those without CKD [3,4]. Several comprehensive registries declare that approximately 30% of ST-segment elevation myocardial infarction (STEMI) and 40% of non-ST-segment elevation myocardial infarction (NSTEMI) patients have CKD [2]. Based on these facts it becomes clear that CKD patients are at a higher risk of suffering from acute coronary syndromes (ACSs) and venous thromboembolisms (VTEs) which require anticoagulation therapy. Additionally these patients are also at an increased risk of bleeding which can be complicated by the use of therapeutic anticoagulants. This study focuses on the use of enoxaparin at therapeutic doses in non-dialysis patients with severe renal impairment or kidney failure.

Classically one of the most frequently used anticoagulants to treat patients with an ACS or a VTE is unfractionated heparin (UFH). However its narrow therapeutic window and the need for frequent monitoring have driven its replacement by low-molecular weight heparins (LMWHs) like enoxaparin. Enoxaparin was first approved in the US in 1993 and differed from UFH by having a longer half-life and a more rapid and predictable absorption without any need for monitoring [5]. Enoxaparin also has a unique mechanism of action in that its inhibitory action against activated factor X is 3-times higher than its inhibitory action against activated factor II (thrombin) [5]. This increased inhibitory activity on activated factor X led to the ability

to monitor enoxaparin's activity by measuring the antifactor Xa activity. Moreover enoxaparin is primarily cleared by the kidneys and thus accumulates in patients with renal impairment. In fact several studies have shown that there is an inverse relationship between the peak antifactor Xa levels and a patient's creatinine clearance (CrCl) when standard therapeutic doses of enoxaparin are given, thus suggesting the need for empiric dose adjustment [6-8]. Additionally several studies found that as CrCl decreases and the antifactor Xa levels increase bleeding rates also increase [8]. However while several large clinical trials have proven the efficacy and safety of enoxaparin in the treatment of VTEs, ACSs, and as bridging therapy for those with atrial fibrillation (AF) at a dose of 1 mg/kg twice daily most of these studies excluded patients with severe renal impairment and to date no large randomized studies have been conducted that assess the safety and efficacy of the drug in this subset of patients.

The manufacturer of enoxaparin suggests that for patients whose CrCl is less than 30 mL/min the therapeutic dose should be reduced to 1 mg/kg once daily [9]. The 2012 Chest guidelines take this recommendation one step further and state that in addition to an empiric dose reduction these patients' antifactor Xa levels should also be monitored at 4 hours after the third dose to avoid drug accumulation [10].

The purpose of this study is to address whether or not antifactor Xa monitoring is necessary in non-dialysis patients whose CrCl is less than 30 mL/min and who are receiving renally adjusted therapeutic doses of enoxaparin.

Methods

Study Design

We conducted this retrospective, observational cohort study at Hendrick Medical Center (HMC), a 522-bed community hospital in Abilene, Texas. The study was approved by HMC and Texas Tech University Health Sciences Center (TTUHSC) institutional review boards. The data was collected in patients who had antifactor Xa monitoring performed between April 2009 and April 2015 from the HMC patient database.

Patient Population

Patients were included if they were adults (≥18 years), had a severe renal impairment (CrCl < 30 mL/min), and received renally adjusted therapeutic enoxaparin doses. A therapeutic renally adjusted enoxaparin dose was defined as 1 mg/kg of total body weight administered once daily [9,10]. Patients included also had to have an appropriate indication for enoxaparin therapy (VTE, AF, or ACS) and had steady-state antifactor Xa peak levels measured [9]. Patients were excluded if they were on dialysis, were pregnant, received enoxaparin doses other than that defined above, or had no antifactor Xa levels collected.

Study Protocol/Sample Collection and Analysis

Based on HMC protocol, patients given a treatment dose of enoxaparin (1 mg/kg SQ daily) and who had severe renal impairment, defined as CrCl < 30 mL/min, have antifactor Xa monitoring performed to obtain steady-state peak levels [9,10]. As recommended by the manufacturer, the antifactor Xa levels are ordered to be collected 4 hours (± 2 hours) after the third dose [9]. The therapeutic antifactor Xa level was defined as 0.5-1.1 units/mL based on the recommendations by Nutescu et al [11].

All antifactor Xa levels were obtained 4 hours (± 2 hours) after the third dose of enoxaparin. Antifactor Xa levels were analyzed using the STA® Rotachrom® Heparin kit on STA-Compact® analyzer. Blood samples are collected in test tubes containing 3.2% sodium citrate, which creates a 9 to 1 blood to anticoagulant mixture. The samples were kept at 68° F (± 9° F) and were analyzed within two hours.

Data Collection

Data was retrospectively collected from HMC's medical records. Lists of patients that were monitored for antifactor Xa levels was obtained. The medical records included information on: age, gender, height, weight, body mass index, serum creatinine (SCr), CrCl, indication, dose, antifactor Xa level, history of bleeding event, hemoglobin, history of transfusion, and time of collection of antifactor Xa level. Baseline data was collected on day one of enoxaparin treatment. History of bleeding events and indications were diagnosed by provider's notation of events in the medical record.

The CrCl for all patients was calculated using the Cockcroft-Gault formula (see below) [12]. Adjusted body weight (AdjBW) was used to calculate CrCl when a patient's total body weight (TBW) was greater than 120% of the patient's ideal body weight (IBW). Otherwise IBW was used to calculate CrCl.

CrCl = (140 - age) x Body weight (kg)/ (SCr x 72) (x 0.85 for females)

AdjBW = IBW + 0.4 (TBW-IBW)

Outcomes

The primary outcome of this study was the proportion of patients whose steady-state antifactor Xa levels were in the therapeutic, subtherapeutic, and supratherapeutic ranges. Subgroup analyses were also performed to assess if antifactor Xa levels differed based on CrCl classification. CrCl data was partitioned into two groups (CrCl ≥ 15 mL/min and CrCl < 15 mL/min). The secondary outcome was the incidence of major bleeding defined as a documented incidence of bleeding in conjunction with either a drop in hemoglobin of > 2 g/dL or a transfusion of ≥ 2 units of packed red blood cells or whole blood.

Statistical Analysis

Descriptive statistics were used to evaluate the number of patients in the therapeutic, subtherapeutic, and supratherapeutic ranges. The percentage of patients within each predetermined antifactor Xa level range was calculated for each population. The Fisher's exact test was applied for nominal data, and Welch's analysis of variance (ANOVA) was applied for continuous data. Pearson and point-biserial correlations were calculated to identify the association of significant baseline characteristics and antifactor Xa levels. A p value less than 0.05 was considered to indicate a statistical significance. Statistical analyses were performed with SPSS, Version 19.0 (IBM Corp., Armonk, NY).

Results

Study Patients

Data was analyzed from a total of 75 patients between April 2009 and April 2015. When the groups were assessed according to antifactor Xa levels 17 patients were subtherapeutic (antifactor Xa levels < 0.5 units/mL), 11 patients were supratherapeutic (antifactor Xa levels > 1.1 units/mL), and 47 patients were therapeutic (antifactor Xa = 0.5-1.1 units/mL), see Table 1. Overall the three subgroups were well balanced based on baseline demographic characteristics (Table 1). The overall average age of patients was 77.4 years (± 12) and approximately 73% were female. Additionally the CrCl did not significantly differ between the three subgroups and the overall average was approximately 20 mL/min (±5).

Characteristic	All Patents n=75 (100%)	Suprathrapeutic n=11 (14.7%)	Subtherapeutic n=17 (22.7%)	Therapeutic n=47 (62.7%)	P value
Male	20 (27)	0 (0)	5 (29)	15 (32)	0.085a
Female	55 (73)	11 (100)	12 (71)	32 (68)	
Age (yrs)	77.4 ± 12.4 (38-95)	79.7 ± 9.8 (61-90)	80.9 ± 8.9 (64-95)	75.6 ± 13.8 (38-95)	0.199 b
Height (cm)	164.0 ± 9.7 (137-193)	162.1 ± 6.3 (155-178)	163.1 ± 9.0 (150-183)	164.8 ± 10.6 (137-193)	0.537 b
Weight (kg)	71.7 ± 23.0 (34-146)	71.1 ± 19.4 (54-120)	64.7 ± 26.1 (34-146)	74.4 ± 22.6 (36-123)	0.415 b
BMI (kg/m2)	26.4 ± 7.6 (13-50)	27.2 ± 8.4 (22-50)	24.0 ± 7.5 (13-44)	27.1 ± 7.4 (16-48)	0.336 b
SCr (mg/dL)	2.6 ± 1.3 (0.7-6.2)	2.3 ± 1.1 (1.2-4.7)	2.3 ± 1.0 (0.7-5.0)	2.8 ± 1.4 (1.0-6.2)	0.184 b
CrCl (mL/min)	20.3 ± 5.2 (8-29)	21.0 ± 6.0 (11-28)	19.8 ± 5.4 (12-29)	20.4 ± 5.1 (8-29)	0.854 b
Antifactor Xa (units/mL)	0.79 ± 0.36 (0.05-2.00)	1.45 ± .28 (1.16-2.00)	0.40 ± 0.13 (0.05-0.49)	0.77 ± 0.17 (0.53-1.08)	<0.001 b
Time to Antifactor Xa collection (hrs)	4.3 ± 0.7 (2.2-6.0)	4.2 ± 0.8 (3.5-6.0)	4.2 ± 0.8 (2.7-5.5)	4.3 ± 0.7 (2.2-6.0)	0.926 b
Enoxaparin Indication					
VTE	10 (13)	1 (9)	1 (6)	8 (17)	0.548a
ACS	39 (52)	5 (45)	8 (47)	26 (55)	
AFIB	26 (35)	5 (45)	8 (47)	13 (28)	

Table 1: Baseline Demographic and Clinical Characteristics of Study Patients. Data are no. (%) of patients or mean ± SD (range values). ACS = acute coronary syndrome; AFIB = atrial fibrillation; BMI = body mass index; CrCl = creatinine clearance; SCr = serum creatinine; VTE = venous thromboembolism; a Fisher's Exact test was utilized for nominal data; b Welch's ANOVA was utilized for continuous data.

Antifactor Xa Monitoring Data

Based on the antifactor Xa level the primary outcome showed that only around 63% of patients were in therapeutic range while 37% of patients were either subtherapeutic (22%) or supratherapeutic (15%). The antifactor Xa level was also assessed for possible correlations with baseline characteristics. And according to this analysis only gender showed a significant association, with males having a significantly lower antifactor Xa level when compared to females (p-value = 0.031). The antifactor Xa level was also assessed according to indication and although the mean antifactor Xa level was higher for those with VTE the difference was not significant (p-value = 0.106). Correlation between antifactor Xa with SCr and CrCl was not significant (Figures 1 and 2). We also performed a further subgroup analysis for those with a CrCl ≥ 15 mL/min (n=63) and those with a CrCl < 15 mL/min (n=12). This subgroup analysis found no difference in regards to antifactor Xa level or any other baseline characteristics with the exception of a significantly higher SCr in those with a CrCl < 15 mL/min (p-value = 0.001) which is to be expected. Furthermore this subgroup analysis indicated that therapeutic antifactor Xa level was not significantly associated with CrCl group.

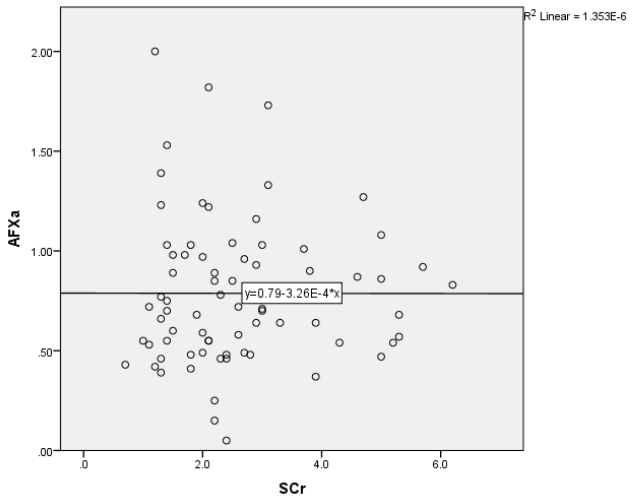

Figure 1: Distribution of antifactor Xa levels according to SCr. No correlation was observed (p-value = 0.992).

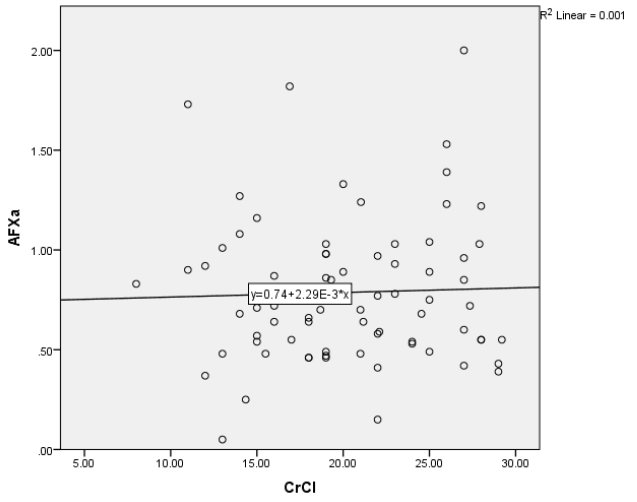

Figure 2: Distribution of antifactor Xa levels according to CrCl. No correlation was observed (p-value = 0.778).

Safety

The rates of bleeding were also assessed according to antifactor Xa level and while multiple patients experienced either a drop in hemoglobin of > 2 g/dL or required a transfusion of ≥ 2 units of packed red blood cells or whole blood, no major bleeding event were documented.

Discussion

Overall this observational study showed that in those with a CrCl < 30 mL/min approximately 37% of patients were not in therapeutic range (0.5-1.1 units/mL). According to the American College of Chest Physicians (ACCP) consensus conference the use of therapeutic enoxaparin in those with a CrCl < 30 mL/min should be accompanied by antifactor Xa level monitoring [8]. The ACCP antithrombotic guideline goes on to say peak antifactor Xa levels should be collected approximately 4 hours after administration [8]. Additionally it states that there is a confirmed linear association between CrCl and antifactor Xa levels after multiple therapeutic enoxaparin doses, and that there is a significant increase in antifactor Xa levels in those whose CrCl < 30 mL/min [8]. Thus our results support the guideline recommendations that antifactor Xa levels should be monitored in patients who have a CrCl < 30 mL/min and are receiving renally adjusted therapeutic doses of enoxaparin.

Almost all of the major clinical trials performed with the use of enoxaparin excluded patients with a CrCl < 30 mL/min and thus there are very few trials that look at the safety and efficacy of enoxaparin when it has been empirically dose adjusted in severe renal impairment. There are even fewer studies that examine the safety and efficacy of enoxaparin in severe renal impairment at the manufacturer recommended dose of 1 mg/kg daily. Lachish et al. is one of the few available studies that does this. In this prospective study of 19 patients with a CrCl < 30 mL/min who received enoxaparin at dose of 1 mg/kg daily 74% of the patients were found to be in therapeutic range (antifactor Xa level = 0.5-1 units/mL) while 26% were not [13]. This study also gives credence to the monitoring recommendations made by the guidelines. Hulot et al. performed a population pharmacokinetic study in non-ST-segment elevation ACS patients [14]. In patients with a CrCl < 30 mL/min receiving an enoxaparin dose of 1 mg/kg daily it was found that this dose successfully avoided drug accumulation and that therapeutic antifactor Xa levels were maintained, however there was a longer period with subtherapeutic levels (< 0.5 units/mL) seen at this dose versus those treated with 1 mg/kg followed by 0.66 mg/kg twice daily dose [14]. Barras et al. confirmed that when enoxaparin is dose adjusted according to renal function then patients were able to successfully achieve and maintain therapeutic antifactor Xa levels [15]. Bazinet et al. performed a prospective trial to compare antifactor Xa levels after 2-3 days of enoxaparin treatment in renally impaired patients versus those without renal impairment [16]. In those who were given 1.5 mg/kg daily there was no statistically significant difference in antifactor Xa levels based on renal function [16]. However when 1 mg/kg twice daily was given the mean levels of antifactor Xa were higher by a statistically significant margin in those with a CrCl ≤ 30 mL/min which translated to having a higher risk of a non-therapeutic antifactor Xa level [16]. These studies along with our current study provide evidence that highlights the need for empiric dose reduction and antifactor Xa monitoring in patients whose CrCl < 30 mL/min.

Besides determining if antifactor Xa level monitoring was necessary in our study population we also wanted to assess the incidence of bleeding and how that correlates with the antifactor Xa level. As previously mentioned renal dysfunction itself is associated with worse outcomes and an increased incidence of bleeding. In fact the GRACE registry (a global registry of acute coronary events) showed that in patients with a CrCl < 30 mL/min there is a significantly increased risk of mortality and major bleeding episodes regardless of the antithrombotic therapies used [17].

In a meta-analysis performed by Lim et al. the use of enoxaparin in non-dialysis patients with severe renal impairment was analyzed to assess bleeding rates. When the standard therapeutic dose of 1 mg/kg twice daily was used the study showed that both the antifactor Xa levels and the bleeding rates were significantly higher in patients with a

CrCl ≤ 30 mL/min than those whose CrCl was higher [18]. However when the enoxaparin dose was empirically adjusted for those with a CrCl ≤ 30 mL/min the antifactor Xa levels were found to be therapeutic and there was no increase in bleeding when compared to those with a higher CrCl [18].

Our study revealed no major bleeding event and so we are not able to discern whether antifactor Xa levels are associated with the rate of bleeding. However a study performed by Montalescot et al. showed that elevated antifactor Xa levels did not predict major bleeding complications and thus the increased bleeding risk in those with reduced renal function might not be resolved with simple dose reduction and antifactor Xa level monitoring [19]. Additionally the study showed that a dose reduction in patients with a CrCl < 30 mL/min allowed antifactor Xa levels to be reached at a similar rate as those seen in patients with a CrCl ≥ 30 mL/min who received a standard enoxaparin dose [19]. Conversely Becker et al. showed that when standard therapeutic doses of enoxaparin were used in NSTEMI and unstable angina (UA) patients with a CrCl < 40 mL/min, higher levels of antifactor Xa were achieved along with an increased incidence of major bleeding, which suggests that antifactor Xa levels do correlate with bleeding risk [20]. Collet et al. looked at the safety and efficacy of enoxaparin in UA and NSTEMI patients with severe renal impairment (CrCl ≤ 30 mL/min). This study found that when the dose was empirically reduced the antifactor Xa levels in these patients were comparable to those without severe renal impairment [21]. It also showed that the bleeding rates did not differ significantly between those with and without severe renal impairment (p-value = 0.53) and thus severe renal impairment was not a predictor of bleeding [21]. This is in direct contrast with other studies that state that renal dysfunction is a predictor of bleeding. Based on these contradictory studies as well as our results it is unclear how antifactor Xa levels correlate with bleeding events and hence requires more investigation.

One of the major strengths of this study is the use of the manufacturer recommended renally adjusted therapeutic enoxaparin dose, which despite its frequent use in practice has not been frequently used in other studies. Another major strength of our study is the exclusive inclusion of a large number of patients with severe renal impairment as compared to other studies. The accuracy of timing of antifactor Xa level collection at our institution with the mean blood collection time being 4 hours after the third dose was also a substantial strength, which provided the appropriate antifactor Xa level interpretation even though this was a retrospective study. However despite the numerous strengths of our study there also exist a few limitations. One of the biggest limitations of this study being the fact that it was only performed at one community hospital and thus its cohort population may not be a true representation of all severe renal impairment patients. Additionally the retrospective design of the study was a limitation which caused a more difficult data collection process as well as created barriers in the analysis of any bleeding events.

Conclusions

To our knowledge this is the largest study performed to date that investigates the necessity of antifactor Xa monitoring in those with severe renal impairment who are treated with the manufacturer recommend dose of 1 mg/kg daily. Based on our results it appears that antifactor Xa monitoring is necessary in non-dialysis patients with a CrCl < 30 mL/min despite renal dose adjustment of enoxaparin to 1 mg/kg daily. Additionally our study shows that antifactor Xa levels do not predict the incidence of bleeding. However there still remains a need for larger studies that more closely analyse the consequences of being outside of therapeutic range for patients with poor renal function and treated with renally adjusted therapeutic doses of enoxaparin. Furthermore future studies should be done to identify optimal dosing strategies for enoxaparin in this patient population.

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