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Correlation of Treatment Dose Enoxaparin with Anti-Xa Concentrations in Adult Hemodialysis Inpatients

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Abstract Enoxaparin, a low-molecular-weight-heparin, is being used in hemodialysis patients despite a lack of guideline or manufacturer dose recommendations. Due to enoxaparin's renal excretion, the possibility of accumulating anti-Xa concentrations in hemodialysis patients using enoxaparin creates a hemorrhagic risk, calling for more research. The objectives of this study are to determine the correlation between treatment dose enoxaparin use and anti-Xa concentrations within the defined therapeutic range in patients receiving chronic, scheduled hemodialysis to determine the degree of change in anti-Xa concentrations in those cases where a concentration was obtained before and after a specific hemodialysis session, and to determine if there is evidence of enoxaparin accumulation over the course of treatment. This was a retrospective cohort study. Patients that were admitted to Indiana University Health facilities in a two-year period were identified from a Cerner query for inclusion eligibility. Inclusion criteria involved patients that received therapeutic dose enoxaparin based on actual body weight on a once daily basis, maintained a scheduled hemodialysis regimen, and had an anti-Xa concentration obtained after at least one enoxaparin dose. Despite lacking statistical significance, the data collected from this study depicts trends which can be utilized to guide future studies. The results of this study suggest that hemodialysis does not effectively remove enoxaparin.

Keywords Enoxaparin, Hemodialysis, Treatment Dose, Correlation, Anti-Xa Concentration, Adult

1. Introduction

Enoxaparin is used increasingly for the treatment of thromboembolic disorders in patients undergoing hemodialysis (HD) despite the lack of manufacturer or guideline recommendations.[1] Enoxaparin offers a more reliable anticoagulant effect than unfractionated heparin (UFH) by having increased, more consistent bioavailability as well as a longer plasma half-life.[2-4] These pharmacological advantages have been found to improve clinical outcomes and are one of the reasons driving the need for additional studies involving treatment dose enoxaparin in hemodialysis.[4]

Enoxaparin is a low-molecular-weight heparin with FDA approved indications for the treatment of acute deep vein thrombosis (DVT) with or without pulmonary embolism (PE), acute ST-segment elevation myocardial infarction (STEMI), unstable angina, and non ST-segment elevation myocardial infarction (STEMI). In addition to treatment, enoxaparin is also FDA approved for the prophylaxis of DVT in medical patients undergoing abdominal surgery, hip replacement surgery, or knee replacement surgery. Enoxaparin achieves anticoagulation by binding to antithrombin III, thus inhibiting clotting factors Xa and thrombin (IIa).[5] Due to enoxaparin's selective nature of inhibiting factor Xa more than IIa, its pharmacokinetics and clinical outcomes may be monitored by measuring a patient's anti-Xa concentrations.

Compared to UFH, enoxaparin primarily undergoes renal elimination. Although routine monitoring of anti-Xa concentrations is not warranted in most patients without renal impairment who are receiving enoxaparin, the possibility of accumulating anti-Xa concentrations in patients with renal dysfunction poses a hemorrhagic risk and therefore is recommended.[6] The ideal time to draw anti-Xa concentrations in patients undergoing HD is at 5 and 24 hours after enoxaparin administration as shown by Overholser [7] and colleagues. Other studies have estimated that it takes seven half-lives, approximately 35 hours, for renally impaired patients to reach steady state, meaning that the ideal time to measure anti-Xa concentrations would be after the second or third dose for patients receiving once-daily treatment.[8,9] The general target range of anti-Xa concentrations is 0.6-1 IU/mL for the 1 mg/kg every 12 hour dosing regimen and 1-2 IU/mL for the 1.5 mg/kg every 24 hour dosing. Of note, the Indiana University Health laboratory uses a target range of 0.6-1.1 IU/mL.[10]

Along with anti-Xa monitoring in patients with renal dysfunction, the 2012 CHEST guidelines recommend a treatment-dose reduction for a creatinine clearance ≤ 30

mL/min to 1 mg/kg every 24 hours based on actual body weight (ABW). However, due to lack of data in patients undergoing HD who are receiving enoxaparin, the guidelines suggest that enoxaparin should not be recommended in these patients, further reinforcing the fact that further study is needed. [11]

Chan [12] and colleagues conducted a retrospective comparative effectiveness study in a large population of chronic maintenance dialysis patients initiated with subcutaneous injections of either enoxaparin or heparin for thromboprophylaxis. The study found that there was no statistically significant increase in serious bleeding or statistically significant decrease in efficacy as compared to subcutaneous heparin. This study combined with the majority of other trials and case reports available only examine prophylactic dose enoxaparin use.[13,14] The following study is the first to examine the potential for drug accumulation of full weight-based, treatment dose enoxaparin in end-stage renal disease (ESRD) patients receiving chronic, scheduled HD, and its influence on bleeding risk and mortality due to inadequate or excessive anticoagulation.

2. Materials and Methods

This was a retrospective cohort study. Patients were identified through a Cerner query of admissions over a two year span from June 1st, 2011 to May 31st, 2013. Any patient that was admitted to an intensive care unit, progressive care unit, or general medical ward at any of the following Indiana University Health facilities was eligible for inclusion: Methodist, University, North, West, and Arnett. Institutional ethical permission was obtained from these facilities. Our initial query identified twenty-three patients eligible for further evaluation.

Patients were included if they received treatment dose enoxaparin at 1mg/kg based on ABW on a once daily basis, were on a scheduled HD regimen, and had an anti-Xa concentration obtained after at least one enoxaparin dose. Patients were required to have a legitimate medical indication for treatment dose enoxaparin and receipt of no other anticoagulant during admission. Exclusion criteria included prisoners, persons <18 years old, active pregnancy, anti-Xa concentration obtained more than 72 hours after last enoxaparin dose, and an enoxaparin dose <1mg/kg daily based on ABW.

The primary study objectives were to determine the correlation between treatment dose enoxaparin use and anti-Xa concentrations within the defined therapeutic range (0.6-1.1 IU/mL) in patients receiving chronic, scheduled HD, to determine the degree of change in anti-Xa concentrations in those cases where a concentration was obtained before and after a specific hemodialysis session, and to determine if there is evidence of enoxaparin accumulation defined by an increase in anti-Xa concentrations over the course of treatment. Secondary study objectives were to assess in-hospital mortality, in-hospital mortality secondary to a venous thromboembolism (VTE)-related complication, and in-hospital mortality secondary to a major bleeding event.

Seven patients were identified for inclusion from the Cerner query. There were sixteen patients that were excluded for eighteen reasons (Table 1). Descriptive statistics were used to present the data which included means and medians. Due to the small sample size and inherent lack of power, p-values were not able to be utilized.

Baseline characteristics are presented in Table 2.

Table 1. Exclusions

Exclusion Criteria	Number of Exclusions
Prisoners	0
Active pregnancy	0
<18 years old	0
Anti-Xa concentration >72 hours after last enoxaparin dose	1
Enoxaparin dose <1mg/kg q24h based on ABW	11
Unscheduled hemodialysis	6
TOTAL	18

Table 2. Baseline Characteristics

	Range	Median
Age (years)	43 - 82	62
LOS (days)	5 – 30	9
ABW (kg)	64 – 98	77
IBW (kg)	50 – 71	57
BMI (kg/m2)	23.6 - 34	31

Six (85.7%) of the seven patients were female. The indications for treatment dose enoxaparin included six patients with a history of VTE and one patient with history of transient ischemic attack. All patients, given that they were on chronic, scheduled HD, were assumed to have ESRD with no remaining residual renal function.

3. Results

The results of this study appear in Table 3 and Table 4. Of the seven patients who met the pre-specified inclusion criteria, one patient (14.3%) was below, four patients (57.1%) were within, and two patients (28.6%) were above the desired anti-Xa range. The correlation coefficient between the daily enoxaparin dose and the first anti-Xa concentration was 0.42. While not statistically significant, this value indicates a "low" (defined as a correlation coefficient between 0.26 and 0.49) correlation between enoxaparin dose and increasing anti-Xa concentration.

Of patients with anti-Xa concentrations above therapeutic range, a median of 9.5 doses of enoxaparin were administered before the concentration was drawn, compared with 1 dose in the subtherapeutic anti-Xa group, and 1.5 doses in the therapeutic range anti-Xa group. Similarly, of the patients with anti-Xa concentrations above range, a median total enoxaparin exposure (number of doses multiplied by enoxaparin dose) of 905 mg was received, compared with 60 mg in the subtherapeutic anti-Xa group, and 140 mg for the within therapeutic range anti-Xa group.

Table 3. Stratified Analysis of 1st Xa Concentration[a]

	Low (n=1)	In Range (n=4)	High (n=2)
ABW (kg)	64.0	88.0 (77 - 98)	67.5 (66 - 69)
Enoxaparin Daily Dose (mg)	60.0	90.0 (80 - 120)	85.0 (70 - 100)
Number of Doses Prior to Concentration	1	1.5 (1 - 2)	9.5 (3 - 16)
Total Enoxaparin Prior to Concentration[b]	60.0	140 (100-160)	905 (210 - 1600)
HD Sessions Prior to Concentration	1 (100%)	1 (25%)	2 (100%)

a – Data presented as median (min, max) or count (percent)
b – Calculated by multiplying enoxaparin daily dose by number of days received

Table 4. Individual Subject Characteristics Stratified by 1st Xa Concentration，Xa Concentration Below Therapeutic Range

	Age (years)	ABW (kg)	Enoxaparin Daily Dose (mg)	Number of Doses Prior	Total Enoxaparin Prior[a]	Number of HD Prior	Xa Concentration (IU/mL)
Subject 1	82	64	60	1	60	1	0.1
Xa Concentration Within Therapeutic Range							
	Age (years)	ABW (kg)	Enoxaparin Daily Dose (mg)	Number of Doses Prior	Total Enoxaparin Prior[a]	Number of HD Prior	Xa Concentration (IU/mL)
Subject 2	62	84	80	2	160	0	0.7
Subject 3	63	77	80	2	160	1	0.6
Subject 4	48	92	100	1	100	0	0.8
Subject 5	53	98	120	1	120	0	0.8
Xa Concentration Above Therapeutic Range							
	Age (years)	ABW (kg)	Enoxaparin Daily Dose (mg)	Number of Doses Prior	Total Enoxaparin Prior[a]	Number of HD Prior	Xa Concentration (IU/mL)
Subject 6	78	69	100	16	1600	7	1.2
Subject 7	43	66	70	3	210	2	1.2

a - Calculated by multiplying enoxaparin daily dose by number of days received

4. Discussion

Due to the small number of patients in the study who met the inclusion criteria, the results of this study fail to achieve statistical significance. However, based on the collected data, several inferences can be made and utilized as hypothesis-generating ideas for future studies.

One trend seen in the collected data is that the ABW of HD patients influenced the likelihood of having an anti-Xa concentration in range. Among those meeting the inclusion criteria of the study, it was found that the patients with higher body weights were more likely to have an anti-Xa concentration within the desired range. Two patients among the three lowest ABW's (66 kg and 69 kg) also had the highest anti-Xa concentrations (both 1.2 units/mL). Since patients with lower body weights were receiving lower daily doses of enoxaparin compared with those with higher body weights, this trend may suggest altered distribution of enoxaparin in HD patients. Future studies should explore the possibility of using doses less than 1 mg/kg of enoxaparin in patients on HD who fall below a defined weight threshold.

Another inference from the study findings involves enoxaparin accumulation in hemodialysis. This was demonstrated by higher anti-Xa concentrations occurring in patients with a higher cumulative number of enoxaparin doses as well as in patients who received more total enoxaparin exposure prior to the first anti-Xa concentration. While three patients who did not receive any HD prior to their first anti-Xa concentration still had an anti-Xa concentration within the target anti-Xa concentration, it should be noted that two of these patients had only received one dose of enoxaparin, and the other patient only received two doses. However, this observation tends to favor the idea that HD doesn't increase the likelihood of having an in-range anti-Xa concentration. Extrapolating from this observation, the data suggests that HD does not effectively remove enoxaparin based on anti-Xa concentrations with regard to daily administration. Therefore, future research should compare pre-HD and post-HD anti-Xa concentrations to more fully and specifically demonstrate the hemodialysis effect on enoxaparin removal to determine if a lower treatment dose of enoxaparin or an extended dosing interval in this patient population may allow for adequate safety and effectiveness.

5. Conclusions

Despite lacking statistical significance, the data collected from this study provides trends which can be utilized to guide future evaluation. The influences on anti-Xa concentrations included patient body weight, number of enoxaparin doses received, and total enoxaparin exposure. The results of this study suggest that hemodialysis does not effectively remove enoxaparin. Future studies should compare pre-HD and post-HD anti-Xa concentrations to more completely define the influence of hemodialysis on enoxaparin clearance.

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