Clinical Review

Anti-Factor Xa Level Monitoring for Enoxaparin Prophylaxis and Treatment in High-Risk Patient Groups

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Abstract

Description

Monitoring anti-factor Xa levels is a controversial topic in the inpatient setting due to resource utilization and unclear conditional guideline recommendations regarding this practice. Enoxaparin dosing in certain high-risk patient populations such as those with low body weight, obesity, renal insufficiency, and pregnancy has not been determined. The objective of this review was to assess the safety and efficacy of enoxaparin monitoring via anti-factor Xa levels in high-risk patient populations.

The PubMed database was searched for articles related to low-molecular-weight heparin monitoring. Randomized controlled trials and meta-analyses that evaluated the safety and efficacy of enoxaparin prophylaxis and treatment in patients with extremes of weight, renal insufficiency, and pregnancy were selected. Fourteen studies representing four high-risk population patient groups were included. Patients with extremes of weight or who were pregnant were found to have subtherapeutic anti-factor Xa levels due to the weight-based dosing of enoxaparin. Those with renal insufficiency were found to be accumulating enoxaparin, indicating the need for a lower dose. Studies have shown that monitoring may be required in specific high-risk patient groups. Dose adjustments based on anti-factor Xa levels can prevent adverse events associated with enoxaparin. Further research involving larger patient populations would be necessary to determine the clinical efficacy of enoxaparin monitoring with anti-factor Xa levels.

Keywords

low-molecular-weight heparin; enoxaparin monitoring; anti-factor Xa monitoring; factor Xa inhibitors; anticoagulants; direct acting oral anticoagulant

Introduction

Monitoring anti-factor Xa levels for enoxaparin is a controversial topic in the inpatient setting due to resource utilization and unclear conditional guideline recommendations regarding this practice. Enoxaparin dosing in certain high-risk patient populations such as those with low body weight, obesity, renal insufficiency, and pregnancy has not been determined. These patient groups may be at an increased risk of bleeding or thromboembolic events.[1] Current studies and guidelines have limited recommendations or guidance on low-molecular-weight heparin (LMWH) monitoring for populations such as patients with extremes of weight, pregnancy, or renal insufficiency. The objective of this review was to assess the safety and efficacy of enoxaparin monitoring via anti-factor Xa levels in high-risk patient populations.

The PubMed database was searched for articles related to LMWH monitoring. Randomized controlled trials and meta-analyses that evaluated the safety and efficacy of enoxaparin prophylaxis and treatment in patients with extremes of weight, renal insufficiency, and pregnancy were selected. Study details, patient characteristics, enoxaparin dosing, and

Table 1. Anti-Factor Xa Goals for Monitoring of Enoxaparin

Indication	Anti-Factor Xa level goal
Prophylaxis	0.2-0.4 units/mL
Therapeutic dosing (1 mg/kg twice daily)	0.5-1 units/mL
Therapeutic dosing (1.5 mg/kg once daily)	1-2 units/mL

outcomes were extracted. Fourteen studies, the manufacturer's instructions, and 2 guidelines were included in this review. The studies included in this review found that patients with extremes of weight or who were pregnant were found to have subtherapeutic anti-factor Xa levels due to the weight-based dosing of enoxaparin. Those with renal insufficiency were found to be accumulating enoxaparin, indicating the need for a lower dose. The studies included in this review will be further elaborated below.

Manufacturer's Instructions

Enoxaparin sodium is a LMWH utilized for the prevention and treatment of venous thromboembolism. This agent works by potentiating antithrombin to inhibit factor IIa and factor Xa in the coagulation cascade. Enoxaparin and other LMWH agents have a measurable surrogate marker in the form of an anti-factor Xa level. The mechanism of action of LMWH makes the anti-factor Xa level a useful measurement for its efficacy. The anti-factor Xa level should be drawn as a peak, 3-5 hours after the third dose of enoxaparin, which should reflect the steady state.[2] The goal anti-factor Xa level is dependent on the indication for receiving enoxaparin (**Table 1**).[3] Monitoring anti-factor Xa levels with enoxaparin is not traditionally done in the inpatient setting because this agent usually has a predictable course of action in the body as it follows first-order elimination pharmacokinetics. Previous clinical trials of enoxaparin reflect this practice.[3] According to the package insert of enoxaparin, the measured mean peak anti-factor Xa levels are 0.16 units/mL following the 20 mg dose and 0.38 units/mL following the 40 mg dose.[1] For patients with unstable angina (n=46) who received 1 mg/kg dose every 12 hours, the mean peak anti-factor Xa level was 1.1 units/mL at steady state, which was achieved on the second day of treatment. While the pharmacokinetics of enoxaparin "appears to be linear over the recommended dosage ranges," the manufacturer of enoxaparin has identified a few key patient groups where this is not true and pharmacokinetics may be altered.[3] The use of enoxaparin in high-risk patient populations such as those with extremes of weight, renal insufficiency, and pregnancy may require laboratory monitoring of anti-factor Xa levels. In patients with renal impairment, an increase in exposure to enoxaparin indicates an increased need for monitoring bleeding signs and symptoms.[3] The package insert for enoxaparin also states that both prophylactic and treatment doses should be adjusted for patients with severe renal impairment, which is defined as a creatinine clearance of less than 30 mL/min. An increase in exposure has been seen in women with weights below 45 kilograms and men weighing less than 57 kilograms. Those patient populations also need to be monitored for signs and symptoms of bleeding. Patients with obesity, defined as a body mass index (BMI) above 30 kg/m^2, are at a higher risk of thromboembolism. The safety and efficacy of prophylactic enoxaparin dosing has not been fully determined and therefore, there is no consensus for adjusting doses in this patient population.

Guideline Recommendations

Monitoring anti-factor Xa levels is a controversial topic in the inpatient setting due to resource utilization and unclear conditional guideline recommendations regarding this practice. There is insufficient data to support the benefit of anti-factor Xa. A previous study has shown some discrepancies in the clinical utility of monitoring anti-factor Xa levels.[4] The 9th edition of the Antithrombotic Therapy and Prevention of Thrombosis guidelines made no recommendation for or against the use of anti-factor Xa monitoring.[2] The published guidelines on Antithrombotic Therapy for Atrial Fibrillation were the first set of guidelines recommending the monitoring of anti-factor Xa.[2] The atrial fibrillation guidelines recommend monitoring pregnant patients receiving a LMWH.[5] There is considerable evidence to support the use of LMWH in high-risk patients, such as those at the extremes of weight and

those with reduced renal function, that can lead to either a subtherapeutic or supratherapeutic anti-factor Xa. However, due to the low certainty in the evidence, the American Society of Hematology (ASH) 2018 guidelines for Management of Venous Thromboembolism did not recommend using anti-factor Xa concentration monitoring to guide enoxaparin dose adjustments in patients with obesity receiving enoxaparin for treatment of venous thrombosis.[6] For patients with renal dysfunction, predefined as a creatinine clearance below 30 mL/min, the ASH guideline panel suggested against using anti-factor Xa concentration monitoring to guide enoxaparin dose adjustments. This suggestion was based upon an analysis of observational studies not included in the evidence profile. That is, 129 of 236 (54.7%) measured peak enoxaparin anti-factor Xa concentrations were found to be within the defined therapeutic range for patients with renal dysfunction (95% confidence index [CI], 48.3%-60.9%).[6] The Journal of Thrombosis and Thrombolysis guidance did not recommend routine monitoring of peak anti-factor Xa levels. However, the journal panel did state that anti-factor Xa level monitoring may be helpful in evaluating safety in high-risk patient populations such as those with severe renal impairment and extremely low body weight.[7]

Patients With Obesity

Obesity causes a hypercoagulable state in which patients are at an increased risk for venous thromboembolism due to inactivity, increased intra-abdominal pressure, chronic low-grade inflammatory state, and impaired fibrinolysis.[8] This is especially apparent in the inpatient setting. Enoxaparin may be eliminated differently in patients with obesity compared with patients of normal BMI and predictable pharmacokinetics. Patients with obesity may have altered pharmacokinetic parameters such as the rate of absorption, volume of distribution, and renal clearance.[1,9] For example, Freeman et al showed that morbidly obese patients (BMI > 40 kg/m^2) receiving enoxaparin for prophylaxis at a fixed dose of 40 mg subcutaneously once daily were more likely to have a subtherapeutic anti-factor Xa. The study compared patients that received a weight-based dose of 0.5 mg/kg, 0.4 mg/kg, or standard 40 mg subcutaneously once daily (80% vs 36% vs 13%; $P < .001$).[10] As a result, Freeman et al concluded that an enoxaparin dose of 0.5 mg/kg daily is superior to either fixed-dose enoxaparin (40 mg daily) or a weight-based regimen of 0.4 mg/kg daily when trying to achieve target peak anti-factor Xa levels in patients with morbid obesity. Limitations of this study included a small sample size and a lack of analysis of clinical outcomes associated with the anti-factor Xa measurements.

Patients With Renal Insufficiency

According to one of the enoxaparin manufacturers, patients with renal insufficiency should receive a lower dose of enoxaparin due to its ability to accumulate in the system. This accumulation can lead to increased exposure and can cause serious adverse events such as bleeding.[3] A meta-analysis by Lim et al showed a positive association between anti-factor Xa and bleeding risk in patients with renal impairment. Specifically, patients with a creatinine clearance of less than 30 mL/min were likely to experience a bleeding event compared to those with a creatinine clearance greater than 30 mL/min (5.4% vs 2.4%, odds ratio 2.25; $P = .013$).[11] Lim et al concluded that empirical dose adjustment of enoxaparin may reduce the risk of bleeding in this patient population.[11] A study performed by Chow et al reflected a similar clinical result. While no bleeding events were reported, a linear correlation between severity of renal failure and anti-factor Xa levels was found ($P < .0005$), indicating that patients with renal insufficiency were accumulating enoxaparin.[12] Dose adjustments should be made prospectively to prevent accumulation and possible bleeding events in this patient population.[12]

Pregnant Patients

According to the Centers for Disease Control and Prevention's (CDC's) Pregnancy Mortality Surveillance System, venous thromboembolism (VTE) is one of the leading causes of maternal mortality in the United States at 9.6%.[13] Pregnancy puts patients at an increased risk of VTE due to increased concentrations of factor VII, factor VIII, factor X, and von Willebrand factor.[14] Pregnant patients have also been shown to have increased fibrinogen concentration.[15] Additionally, patients may experience more immobility during pregnancy, which can contribute to venous stasis.[15] The pharmacokinetics

of pregnant women are altered which can make dosing medications, particularly anticoagulants, difficult.[16,17] Friedrich and Hameed conducted a prospective, cross-sectional pilot project in which 15 pregnant subjects received therapeutic doses of enoxaparin at a dose of 1 mg/kg twice daily.[18] The study showed that 73% of the trough anti-factor Xa levels were determined to be subtherapeutic. The clinical ramifications of these subtherapeutic anticoagulant levels remain uncertain. Friedrich and Hameed's study had a small sample size (n=15) and most of the subjects were obese in addition to being pregnant. This literature review awaits additional trials on pregnant patients before recommendations are made.

Patients With Low Body Weight

Enoxaparin is dosed based on the patient's total body weight for both prophylaxis and treatment dosing. Sacha et al demonstrated that underweight patients (< 45 kg) were more likely to have subtherapeutic anti-factor Xa levels likely due to weight-based dosing.[1] Despite the subtherapeutic anti-factor Xa levels, 6 patients in this study had bleeding events while on enoxaparin. Another study conducted by Rojas et al examined the results for patients weighing less than 55 kilograms who received enoxaparin prophylaxis at a dose of 40 mg/day.[19] Body weight was shown to be inversely correlated with anti-factor Xa level. Anti-factor Xa level decreased for each kilogram of weight by 0.0121 IU/ml (95% CI, -0.02 to –0.005).[19] The studies on patients with low body weight have small sample sizes, therefore, recommendations remain inconclusive.

Conclusion

When used appropriately, enoxaparin is a safe and effective option for both prophylaxis and treatment of venous thromboembolism. The predictable and linear pharmacokinetic properties allow a lack of monitoring for patients with normal weight and renal function.[3] However, studies have shown that monitoring may be required in specific high-risk patient groups. These high-risk patient groups include patients with extremes of weight, those with renal insufficiency, and pregnant patients. Anti-factor Xa level monitoring is a useful tool to inform whether a patient is adequately anticoagulated. Dose adjustments based on anti-factor Xa levels can prevent adverse events associated with enoxaparin, such as bleeding. Pharmacists are in an excellent position to provide monitoring of enoxaparin in the hospital setting. There is insufficient evidence to make inferences about monitoring anti-factor Xa levels on high-risk patients receiving a LMWH. Further research involving larger patient populations would be necessary to determine the clinical efficacy of enoxaparin monitoring with anti-factor Xa levels.

Conflicts of Interest

The author declares that they have no conflicts of interest.

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