Dosing of Enoxaparin in Renal Impairment

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ABSTRACT

Objective: To review enoxaparin treatment dosing, pharmacokinetics, and clinical outcomes data in patients with renal impairment and to examine the current two-tiered dosing regimen approved by the Food and Drug Administration (FDA).

Data Sources: A literature search of PubMed (1990–2016) was performed using the search terms *low-molecular-weight heparin, unfractionated heparin, bleeding, enoxaparin, renal impairment, pharmacokinetics,* and *hemodialysis.*

Study Selection and Data Extraction: All studies assessing the pharmacokinetic properties of enoxaparin in patients with renal impairment were evaluated. In addition, all retrospective and prospective studies assessing the safety and efficacy of enoxaparin treatment in this population were evaluated.

Data Synthesis: Five pharmacokinetic studies evaluated changes in the pharmacokinetics of enoxaparin in patients with renal impairment. In these studies, enoxaparin clearance was reduced by 17% to 44% in patients with mild and moderate renal impairment. Six retrospective studies evaluated the safety of enoxaparin in patients with renal impairment. In one study, patients with moderate renal impairment were at increased risk of bleeding when using the current FDA-approved two-tiered scheme (odds ratio, 4.7; 95% confidence interval, 1.7–13.0; $P = 0.002$). Another study demonstrated that individualized enoxaparin dosing, when compared to FDA-approved dosing, resulted in a decreased risk of bleeding. Two retrospective studies evaluated efficacy. One of these studies compared reduced-dose enoxaparin with unfractionated heparin; there was a trend toward lower incidences of thromboembolism and 30-day mortality with reduced-dose enoxaparin. Hospital length of stay also decreased with reduced-dosed enoxaparin.

Conclusions: This paper highlights the differences in the pharmacokinetic properties and safety and efficacy outcomes in multiple degrees of renal impairment when using treatment-dose enoxaparin. Given the literature highlighted in this review, a more multitiered enoxaparin renal dosing strategy—perhaps shifting from the current two-tier approach to at least three or four tiers—should be considered.

Keywords: low-molecular-weight heparin, unfractionated heparin, bleeding, enoxaparin, renal impairment, pharmacokinetics, hemodialysis

INTRODUCTION

The Food and Drug Administration (FDA) approved enoxaparin (Lovenox, Sanofi-Aventis U.S.), a low-molecular-weight heparin (LMWH), in 1993. Since then multiple generic versions of the drug have been approved as well.[1] In general, LMWH agents have been shown to be noninferior to unfractionated heparin (UFH) for the treatment of deep vein thrombosis and pulmonary embolism, and they have largely replaced UFH in many niches for a variety of practical reasons.

LMWHs are fragments of UFH, a heterogeneous mixture of sulfated glycosaminoglycans, and are approximately one-third the molecular weight of UFH.[2] Enoxaparin exhibits anti-coagulant properties similar to UFH by binding to and accelerating the activity of antithrombin III, which further inactivates thrombin (factor IIa) and factor Xa. However, LMWHs exhibit a much greater and specific effect on factor Xa than on thrombin. This difference is a result of the shorter pentasaccharide structure and smaller molecular size of LMWH, which makes it less likely to form a ternary complex necessary for thrombin inhibition.[3]

There are distinct advantages to the use of LMWHs instead of UFH. LMWHs have a more predictable anticoagulant response, improved subcutaneous bioavailability, dose-independent clearance, longer biological half-life, and a lower incidence of thrombocytopenia.[2] Elimination of LMWHs also differs from UFH in that LMWHs are primarily renally eliminated. In contrast, UFH exhibits saturable and nonsaturable mechanisms and is primarily metabolized in the liver and reticuloendothelial system.[4]

Given the renal elimination of LMWHs, the 2012 CHEST guidelines on antithrombotic therapy and prevention of thrombosis raise concerns regarding the accumulation of the drug and increased bleeding risks with LMWHs in patients with renal dysfunction.[5] Furthermore, the American College of Chest Physicians developed a consensus statement recommending the following approaches to dosing LMWH in chronic kidney disease: The use of UFH is preferred over LMWH. If LMWH is chosen, anti-Xa monitoring and/or dose reduction is recommended, and enoxaparin 1 mg/kg once daily may be given.[5] Similarly, enoxaparin prescribing information does not delineate dosing recommendations for patients with a creatinine clearance (CrCl) of 15–29 mL/min compared with those whose CrCl is less than 15 mL/min, thus possibly resulting in apprehension among practitioners about the use of enoxaparin in patients with severe renal impairment.[6] As discussed in subsequent portions of this paper, this safety dilemma also extends to patients with moderate renal impairment (CrCl of 30–50 mL/min), who, under the current FDA labeling, are not considered for dose reductions.

To ensure appropriate dosing and to increase safety and efficacy of enoxaparin use in renal failure, obesity, and pregnancy, the measurement of antifactor Xa (anti-Xa) concentrations is recommended, and therapeutic goals have been established. The therapeutic range used by many institutions has been largely based on evidence from multiple clinical trials, including the Thrombolysis in Myocardial Infarction

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Dosing of Enoxaparin in Renal Impairment

(TIMI) 11A study, which evaluated the difference in safety and efficacy outcomes between enoxaparin 1.0 mg/kg and 1.25 mg/kg twice daily in patients with unstable angina/non-ST segment elevation myocardial infarction (NSTEMI).[7] This study showed that using a peak anti-Xa concentration goal between 0.5 and 1.0 IU/mL when administering enoxaparin 1.0 mg/kg twice daily resulted in reduced rates of recurrent acute coronary syndrome and mortality, similar to enoxaparin 1.25 mg/kg twice daily. Furthermore, maintaining peak anti-Xa concentrations within 0.5–1.0 IU/mL resulted in fewer bleeding events.[7]

Many pharmacokinetic and outcomes studies suggest adjustments of enoxaparin treatment dosing beyond what is recommended by the FDA and CHEST guidelines. This article will summarize the evidence for the safe and effective use of enoxaparin treatment dosing in patients with renal impairment. This paper aims to present literature that supports the need for further dose adjustment of enoxaparin in patients with renal impairment. However, given the lack of robust and well-designed studies, dosing recommendations beyond those approved by the FDA cannot be made at this time.

FDA-APPROVED DOSING AND LABORATORY MONITORING

The prescribing information for enoxaparin provides therapeutic dosing recommendations based on renal function (Table 1). However, it utilizes only two tiers: CrCl of 30 mL/min or greater and CrCl of less than 30 mL/min.[6]

Current guidelines suggest target peak anti-Xa concentrations of 1.0–2.0 IU/mL if the medication is administered every 24 hours and 0.5–1.0 IU/mL if dosing takes place every 12 hours. Peak concentrations should be drawn four to six hours after the third dose of enoxaparin. At present, there is no high-level evidence to suggest or recommend an optimal anti-Xa trough level goal in patients with a CrCl of less than 30 mL/min.[8]

PHARMACODYNAMICS AND PHARMACOKINETICS IN THE GENERAL POPULATION

The pharmacokinetic properties of absorption, distribution, metabolism, and excretion differ between UFH and LMWH. A study by Bendetowicz et al. demonstrated that an injection of 40 mg of enoxaparin resulted in twice as many heparin molecules reaching systemic circulation compared with administration of 5,000 units of UFH.[9] Although the bioavailability of UFH versus LMWH does not significantly affect prescribing, the variability in the effect of UFH is a reasonable consideration when deciding which heparin product to use. UFH has high variability in effect, which requires frequent laboratory monitoring, whereas LMWH has significantly less variability. A study by Rabah et al. showed adequate anti-Xa concentrations in all 30 patients who received a single dose of enoxaparin 1 mg/kg compared with patients who received UFH, 30% of whom needed additional titration to reach a desired effect.[10]

Enoxaparin elimination takes place completely through a nonsaturable, linear renal mechanism, following first-order kinetics.[4,10] Because of the extended half-life of enoxaparin compared with UFH, enoxaparin requires less frequent administration. In addition, LMWH has more "dose predictability" than UFH due to lower protein binding, relatively constant half-life irrespective of dosing, and an area under the curve that increases linearly with dose.[11] However, given the risk for accumulation and subsequent bleeding risk, the extended half-life of enoxaparin can also be viewed as a disadvantage in patients with renal impairment. A multitiered dosing approach to enoxaparin may help mitigate this disadvantage by optimizing both safety and efficacy.

PHARMACOKINETICS IN PATIENTS WITH RENAL IMPAIRMENT

Cadroy and colleagues observed 12 patients with chronic renal impairment (mean age, 58 years) and 12 healthy volunteers (mean age, 23 years) to compare the pharmacokinetic differences between these populations after a single subcutaneous enoxaparin injection of 0.5 mg/kg. The CrCl of those with renal impairment ranged from 5 to 21 mL/min (mean, 11.4 mL/min). These patients were compared with healthy individuals who had a CrCl ranging from 88 to 140 mL/min (mean, 105 mL/min).[12]

Pharmacokinetic parameters in the statistical analysis included the observed maximal concentration (C_{max}), time of maximal concentration, the elimination half-life, the area under anti-Xa activity-time curve, mean residence time, the clearance of elimination, and the distribution volume, all of which were calculated using an anti-factor Xa activity disappearance curve. The clearance was 1.9 times lower ($P < 0.001$) and the elimination half-life was 1.7 times longer ($P = 0.01$) in patients with chronic renal failure. The C_{max} was slightly but significantly higher in patients with chronic renal failure, and it was reached 30 minutes later ($P = 0.05$). The volume of distribution was similar in both groups.[12]

The TIMI 11A study used a population pharmacokinetic analysis to evaluate the safety and tolerability of two weight-adjusted enoxaparin regimens in patients with unstable angina and NSTEMI. Based on this model, a "typical" patient with median weight and median CrCl would have an enoxaparin clearance of 0.733 L/hour, a volume of distribution of 5.241 L, and a half-life of five hours. This study showed that enoxaparin clearance was significantly related to patient weight and CrCl and was the only consistent predictor of hemorrhagic events.[7]

Table 1 Enoxaparin Dosing Recommendations From Prescribing Information[6]		
Indication	**Creatinine Clearance**	
	≥ 30 mL/min	**< 30 mL/min**
Inpatient treatment of acute DVT with or without pulmonary embolism	1 mg/kg SC every 12 hours or 1.5 mg/kg SC once daily	1 mg/kg SC once daily
Outpatient treatment of acute DVT without pulmonary embolism	1 mg/kg SC every 12 hours	1 mg/kg SC once daily
Prophylaxis of ischemic complications of unstable angina and non-ST segment elevation myocardial infarction	1 mg/kg SC every 12 hours	1 mg/kg SC once daily
DVT = deep vein thrombosis; SC = subcutaneously		

Dosing of Enoxaparin in Renal Impairment

Bruno and colleagues performed a pharmacokinetic analysis based on TIMI 11A and found that a CrCl of 30 mL/min decreased enoxaparin clearance by 27% compared with a median CrCl of 88 mL/min and was also related to a predicted 3.8-fold increase in the risk of major hemorrhagic episodes. A CrCl of 50 mL/min also decreased enoxaparin clearance by 17% compared with that in patients with a median CrCl of 88 mL/min. Of note, the increased risk of hemorrhagic episodes was based on a pharmacokinetic/pharmacodynamic model and not actual observed events in patients, which is a significant limitation of this study.[13]

Current FDA labeling and CHEST guidelines suggest enoxaparin dose adjustments when CrCl is less than 30 mL/min to reduce the risk of accumulation and bleeding.[5,6] However, much consideration needs to be given to whether this is the optimal cutoff point for patients with renal impairment. A population pharmacokinetic analysis by Hulot and colleagues showed that the clearance of enoxaparin was reduced by 31% in patients with moderate renal impairment (CrCl of 30–49 mL/min) and by 44% in patients with severe renal impairment (CrCl less than 30 mL/min).[14] The reduced clearance could result in significant accumulation, which provides a basis for the need to adjust enoxaparin beginning at a CrCl of less than 50 mL/min.

SAFETY OF UNADJUSTED ENOXAPARIN IN RENAL IMPAIRMENT

Evidence supports the premise that enoxaparin and UFH are associated with comparable bleeding risks. A retrospective cohort study by Thorevska et al. showed that twice-daily enoxaparin and UFH regimens were associated with comparable increases in major bleeding complications in patients with mild, moderate, or severe renal impairment.[15]

Another retrospective analysis of patients with severe renal impairment by Spinler et al. reached similar conclusions based on an examination of the ESSENCE and TIMI 11B studies. The safety outcome identified in this study was major hemorrhage, defined as bleeding resulting in death; a bleed that was retroperitoneal, intracranial, or intraocular; a drop in hemoglobin concentration of 3 g/dL or greater; or the need for two or more units of transfused blood. There was no statistically significant difference in the rate of major hemorrhage in patients with severe renal impairment (CrCl of 30 mL/min or less) between UFH and enoxaparin 1 mg/kg twice daily. However, in a subgroup analysis of patients with severe renal impairment (CrCl of 30 mL/min or less) and without severe renal impairment (CrCl greater than 30 mL/min), there was a statistically significant increase in major bleeding in both the UFH and enoxaparin groups who had severe renal impairment. It is evident that the risk of bleeding exists with both UFH and enoxaparin in patients with renal impairment. Furthermore, in the enoxaparin arm, as the degree of renal impairment worsened, the risk of bleeding increased.[16]

Another study suggests that the two-tiered dosing guidelines may not be adequate for optimizing the safety of patients with moderate renal impairment. A retrospective review conducted by DeCarolis and colleagues compared once-daily and twice-daily enoxaparin dosing in patients with normal renal function (CrCl greater than 80 mL/min) with those with moderate renal impairment (CrCl of 30–50 mL/min). There was an increased risk of major bleeding in patients with moderate renal impairment compared with those whose CrCl exceeded 50 mL/min.[17] This was an adequately sized, well-designed study. However, it was limited by retrospective data collection and potential bias without proper randomization because the decision to use enoxaparin was not controlled. In addition, the external validity of the results is limited because the study was conducted at a Veterans Administration Medical Center. The reported bleeding episodes included occurrences following cardiac ablation procedures, which confounded the results.[17]

Bleeding risk associated with enoxaparin 1 mg/kg daily in patients with stage 4 or 5 chronic kidney disease was determined in a prospective study by Lachish et al. Among the 19 patients enrolled in this study, no major bleeding events occurred during the three-day study period, which purportedly supported the current FDA recommendation. However, this was a short-term study of hospitalized patients, and the study was not powered to show a statistically significant risk of bleeding.[18]

In summary, multiple sources confirm that use of enoxaparin results in an increased risk of bleeding in patients with renal impairment. These safety studies seem to provide the impetus for fine-tuning renal dosing guidelines to varying degrees of renal impairment with CrCl of less than 50 mL/min.

OUTCOMES WITH DOSE-ADJUSTED ENOXAPARIN

Product-label enoxaparin dosing has been shown to increase the risk for bleeding in patients with moderate renal failure. However, some studies have shown the safe and efficacious use of adjusted enoxaparin dosing for thromboembolic complications in patients with varying degrees of renal impairment.

The Collet report was the first piece of literature to critique FDA dosing recommendations in a study observing outcomes with dose-adjusted enoxaparin in patients with renal impairment. As described in this letter to the editor, patients with unstable angina or NSTEMI from the TIMI 11A study were treated with aspirin and enoxaparin. Patients with normal renal function (CrCl greater than 60 mL/min) received 1 mg/kg of enoxaparin every 12 hours and achieved an anti-Xa level of 1.01 ± 0.05. To achieve a similar anti-Xa level, patients with moderate renal failure (CrCl of 60 mL/min to less than 30 mL/min) received an average dose of 0.84 ± 0.03 mg/kg every 12 hours. In patients with severe renal failure (CrCl less than 30 mL/min), a dose of 0.64 ± 0.04 mg/kg achieved an anti-Xa level of 0.95 ± 0.07. There were no reports of major bleeding in the patients with severe renal failure receiving enoxaparin. This report offers some evidence for the safe and effective administration of enoxaparin with further dose adjustments in patients with moderate and severe renal impairment.[19]

A pharmacokinetic program created at Palomar Medical Center was used to address adverse bleeding events for renally impaired patients on enoxaparin. One hundred seventy patients were analyzed using an enoxaparin renal dosing protocol to describe an empiric dosing strategy in response to anti-Xa concentrations. Patients with orders for enoxaparin 1 mg/kg twice daily or 1.5 mg/kg once daily were screened for renal impairment using the Cockroft-Gault equation. Patients were

grouped into moderate renal impairment (CrCl 30–60 mL/min) or severe renal impairment (CrCl 30 mL/min or less). An anti-factor Xa goal of 0.60–1.00 IU/mL was adopted as the target based upon 2001 guidelines from the American College of Chest Physicians and 1998 guidelines from the College of American Pathologists.[20]

All patients were administered a subcutaneous enoxaparin loading dose of 1 mg/kg. Patients who were prescribed 1.5 mg/kg daily were switched to 1 mg/kg. The maintenance doses were modified by pharmacists based on the Collet report, with modifications made based on clinical judgment. Those with moderate renal impairment continued with 0.75 mg/kg every 12 hours, and patients with severe renal impairment continued with 0.50 mg/kg every 12 hours. In patients with anti-Xa concentrations outside of the therapeutic range of 0.60–1.00 IU/mL, doses were adjusted with the following ratio using a goal anti-Xa level of 0.80 IU/mL:

(Current Dose)/(Current Anti-Xa) = (New Dose)/(Goal Anti-Xa).

The results of the study showed that the anti-Xa concentrations fell within the therapeutic range for both specified groups with dose adjustments. The mean anti-Xa level in the severe renal impairment group after a dose adjustment was 0.71 ± 0.13 (95% confidence interval [CI], 0.61–0.82). The mean anti-Xa level in the moderate renal impairment group after a dose adjustment was 0.86 ± 0.03 (95% CI, 0.81–0.92). Moreover, there was only one incidence of minor bleeding in the severe renal impairment group. These results suggest that multiple-tiered enoxaparin dosing adjustments in patients with renal impairment can result in consistent attainment of therapeutic anti-Xa concentrations.[20]

Because of the hesitancy to use enoxaparin in patients on hemodialysis, this population has traditionally been treated with UFH. A single-center retrospective chart review at the University of California Davis Medical Center was conducted to evaluate the outcomes associated with use of reduced-dose therapeutic enoxaparin versus continuous-infusion intravenous UFH for anticoagulation in hemodialysis patients.[21] Patients were matched 1:1 based on anticoagulation indication, with a majority of patients being treated for venous thromboembolism (VTE). After exclusion for various reasons, 164 patients were included in this study, with 82 patients in each group. The average daily dose of enoxaparin administered was 0.7 mg/kg per day (range, 0.4–1.0 mg/kg per day). There was no statistically significant difference in the incidence of 30-day thromboembolic events (0% versus 2.44%; $P = 0.5$) or in the incidence of major bleeding (6.1% versus 11%; $P = 0.4$) for enoxaparin compared with UFH, respectively. However, the incidence of 30-day thromboembolic events and major bleeding was lower in the enoxaparin group. Although the results were not statistically significant, there may be some utility for using enoxaparin in this patient population. Secondary outcomes assessed hospital length of stay, mortality, and readmission rates. Enoxaparin administration was associated with a shorter hospital length of stay compared with UFH (20 ± 53.8 days versus 28.9 ± 44.5 days; $P = 0.02$).[21] Although this was statistically significant, large standard deviations were associated with the length of stay in both groups. These results show promise for the safe and effective use of enoxaparin in

hemodialysis patients, potentially allowing shorter hospital stays and similar, if not lower, incidences of bleeding and thromboembolic events.

BLEEDING EVENTS WITH DOSE-ADJUSTED ENOXAPARIN

Enoxaparin dosing recommendations approved by the FDA have been shown to be associated with an increased incidence of bleeding in patients with renal impairment.[15–18] The evidence has led to several studies using dose-adjusted enoxaparin to minimize the risk of bleeding in this patient population. A retrospective evaluation by Kruse and Lee[20] found that the incidence of bleeding in patients with moderate renal impairment was comparable to patients with normal renal function in the ELECT and PCI trials. Patients with moderate renal impairment and severe renal impairment received enoxaparin dosed daily at 0.75 mg/kg and 0.5 mg/kg, respectively, with dose adjustments using a generated equation targeting an anti-Xa level of 0.8 IU/mL.

A prospective randomized study by Barras et al.[22] compared bleeding events in conventional (product-label) enoxaparin dosing to individualized dosing. Patients in the individualized group received enoxaparin based initially on weight following the degree of renal impairment, starting at a CrCl of less than 50 mL/min. Patients weighing less than 100 kg were dosed according to total body weight, and patients weighing 100 kg or more were dosed according to lean body weight. The dosing scheme followed by the authors included the following fractions of the usual daily dose based on CrCl:

- 50 mL/min or greater = 1.0 mg/kg
- 40–49 mL/min = 0.6 mg/kg
- 30–39 mL/min = 0.5 mg/kg
- 20–29 mL/min = 0.4 mg/kg
- 10–19 mL/min = 0.3 mg/kg

A major bleed was defined by a decrease in hemoglobin of more than 30 g/L or evidence of an internal anatomical bleed. A minor bleed was defined as any other bleed, such as hematemesis, epistaxis, hematuria, or an injection or veni-puncture site bleed. Of the 31 patients with a CrCl less than 50 mL/min, five patients had a primary event of bleeding (four [23%] in the conventional arm versus one [7%] in the individualized arm). Six patients (12%) in the individualized arm and 21 (40%) in the conventional arm had a secondary event, defined as composite bleeding and bruising (relative risk [RR], 0.30; 95% CI, 0.12–0.71; $P = 0.003$). In both arms, there were no recurrent thromboembolic events during treatment and no deaths occurred at 30 days. In sum, 122 patients were studied, and patients in the individualized dosing group had fewer bleeding events (RR, 0.12; 95% CI, 0.12–0.72; $P = 0.003$).[22] From the results of this study, we can infer that patient safety may be compromised without further dose adjustment of enoxaparin starting at a CrCl of less than 50 mL/min.

Safety data related to enoxaparin use in hemodialysis patients is limited. Thus far, only one study is available on the use of dose-adjusted enoxaparin in patients on various types of hemodialysis. A retrospective chart review by Pon et al.[21] showed no statistically significant difference in the incidence of major bleed-

ing in hemodialysis patients between UFH and dose-adjusted enoxaparin (11% versus 6.1%; P = 0.4). Patients in the enoxaparin group largely received intermittent hemodialysis compared with the UFH arm (95.1% versus 84.2%; P = 0.03). Other methods of dialysis that patients received in this study included peritoneal dialysis, slow-extended daily dialysis, and continuous renal replacement therapy. The average enoxaparin dose administered was 0.7 mg/kg per day (range 0.4–1.0 mg/kg per day). The data suggested that enoxaparin can be used safely in patients on hemodialysis when dosed appropriately and may be comparable to UFH. Pon et al.[21] also examined secondary endpoints, including length of hospital stay, 30-day readmission rates, and 30-day mortality. The study showed that hemodialysis patients treated with enoxaparin at an average dose of 0.7 mg/kg had a shorter mean length of hospital stay than patients treated with therapeutic UFH (20.0 days versus 28.9 days; P = 0.02).

CONCLUSION

Despite the benefits seen in using enoxaparin rather than UFH in treating VTE, enoxaparin's relatively high degree of renal excretion raises a concern for drug accumulation and a commensurate increased bleeding risk in patients with renal impairment. These pharmacokinetic properties led to an FDA-approved two-tiered dosing strategy with a CrCl cutoff of 30 mL/min; however, both pharmacokinetic and outcomes data seem to demonstrate that enoxaparin could be used even more effectively and safely with a multitiered enoxaparin renal dosing strategy. Lower doses should be used for populations in the 30 mL/min to 50 or 60 mL/min CrCl range and in the less than 15 mL/min range. However, additional data may be needed to more definitively refine renal dosing guidelines beyond what is currently approved by the FDA.

Understanding the available data when dosing enoxaparin in patients with renal impairment is crucial to patient safety. Dose-adjusted enoxaparin may be used effectively and safely for thromboembolic complications in patients with renal impairment and could result in an overall decline in health care expenditures, especially by decreasing the length of hospital stay. Larger controlled trials are needed to definitively establish the role and methods of using enoxaparin for VTE with further dose adjustments in patients with varying degrees of renal impairment.

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