Individualized Dosing of Enoxaparin for Subjects With Renal Impairment Is Superior to Conventional Dosing at Achieving Therapeutic Concentrations

Michael A. Barras, BPharm,*† Stephen B. Duffull, PhD,‡ John J. Atherton, PhD,§‖ and Bruce Green, DClinPharm¶

Introduction: Enoxaparin is an anticoagulant used in the treatment of thromboembolic diseases. It is a hydrophilic molecule that is, predominantly, eliminated renally with few data to support dosing for subjects with renal impairment and/or obesity. A recently conducted randomized controlled clinical trial compared individualized enoxaparin doses based on lean body weight and renal function to conventional dosing. During this trial, anti-Xa concentrations were collected using a sparse sampling design and a population pharmacokinetic model was developed to describe the data.

Methods: The current study evaluated the ability of the individualized dose to achieve and maintain anti-Xa concentrations within the therapeutic range (0.5–1.0 IU/mL) in subjects with renal impairment and/or obesity. A matched comparison of the two dosing strategies was undertaken using individual model predicted anti-Xa concentrations generated every 30 minutes to 120 hours post initiation of therapy. Concentration–time curves were generated for each subject and the proportion of time in the therapeutic, supra-therapeutic, and subtherapeutic ranges were determined.

Results: When compared with conventional dosing, individualized dosing in subjects with renal impairment resulted in a significantly greater proportion of time in the therapeutic range (median [range] = 69.9% [11.3–91.8] versus 42.6% [13.9–71.4], P = 0.02) and a significantly reduced proportion of time in the supratherapeutic range (median [range] = 9.3% [0%–67.0%] versus 37.1% [0%–85.7%], P = 0.02). Although there was a trend toward a greater proportion of time in the therapeutic range in obese subjects, this did not achieve statistical significance.

Conclusions: Individualized dosing in subjects with renal impairment is more effective than conventional dosing at achieving and maintaining therapeutic anti-Xa concentrations, which could decrease the risk of bleeding events and mortality in these subjects.

Key Words: dose-individualization, therapeutic range, enoxaparin, renal disease, obesity, NONMEM, therapeutic drug monitoring

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INTRODUCTION

Enoxaparin is a low-molecular-weight heparin proven to be as effective as unfractionated heparin in Phase III clinical trials and postmarketing studies for the treatment of acute coronary syndromes, pulmonary embolism, and deep vein thrombosis. The approved labeled dose is 1.0 mg/kg twice a day or 1.5 mg/kg once a day with a dose reduction to 1.0 mg/kg once a day for subjects with an estimated creatinine clearance (CLcr) less than 30 mL/min. Total body weight (TBW) is the body size descriptor recommended for all dose calculations.

The therapeutic range for enoxaparin originated from the Thrombolysis in Myocardial Infarction (TIMI) 11A study, which provided evidence that antiactivated Factor X (aXa)-concentrations between 0.5 and 1.0 IU/mL minimized bleeding events while maintaining effectiveness. In this study, doses of 1.25 mg/kg twice daily were shown to increase plasma aXa concentrations significantly and major bleeding events when compared with 1.0 mg/kg twice a day with no reduction in recurrent acute coronary syndrome or mortality. Similarly, Montelecot et al reported that subjects with peak aXa concentrations less than 0.5 IU/mL, measured 4 to 6 hours postdose, had a threefold increase in 30-day mortality compared to subjects with aXa concentrations between 0.5 and 1.2 IU/mL, further supporting the therapeutic range.

Clearance (CL) of enoxaparin has been described as a function of both renal elimination and nonrenal metabolism. Because these processes have been shown to be proportional to lean body weight (LBW), subjects with renal impairment and/or obesity who are administered enoxaparin according to the product label (PL) are at risk of supratherapeutic aXa concentrations, leading to excessive Factor Xa inhibition and bleeding. In an attempt to reduce these risks, clinicians often elect to arbitrarily cap the dose, adjust the dose to the therapeutic range, or choose another anticoagulant.

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To assess the clinical impact of the apparent scientific deficiency of the PL, an individualized dose strategy was recently compared with conventional dosing in a prospective, randomized controlled trial (RCT). Briefly, data were collected during time windows determined using LBW in the C-G equation. However, the ability of the individualized dose strategy to achieve and maintain therapeutic aXa concentrations, particularly in subjects with renal impairment and/or obesity, was not evaluated. The aim of this study was to evaluate the ability of an individualized dosing strategy to maintain a therapeutic range over a 120-hour treatment period in comparison with conventional dosing.

MATERIALS AND METHODS

Previous Studies

An extensive description of data used for this study has been published elsewhere. Briefly, data were collected during a prospective RCT in which subjects were stratified to receive either an individualized or conventional dose regimen of enoxaparin. Subjects in the individualized arm were administered subcutaneous enoxaparin at a dose of 1.0 mg/kg twice a day (TBW) unless they had a TBW 100 kg or greater (considered obese), in which case they were dosed at 1.5 mg/kg twice a day using LBW. Subjects with an estimated CL\textsubscript{CR} less than 50 mL/min (considered to have renal impairment), calculated using the Cockcroft-Gault (C-G) equation, in which ideal body weight was substituted for TBW, were dosed at 1.0 mg/kg twice a day for 2 days and then according to a reduction regimen shown in Table 1. Subjects in the conventional arm received doses selected by the prescriber (PL based dosing).

Because enoxaparin is a mixture of molecules of varying molecular weights, aXa concentrations were used as a marker of enoxaparin concentrations. Plasma aXa concentrations were collected during time windows determined using D-optimality to help ensure pharmacokinetic (PK) parameters could be estimated with good precision. The nominal design required three samples per patient taken at between 15 to 30 minutes, 60 to 120 minutes, and 180 to 300 minutes post-dose. A total of 118 patients provided 349 aXa concentrations. Dots represent data points; solid line represents the unity line and dashed line represents the smooth line. However, plots relevant to this current study are provided. The individual model predicted aXa concentrations closely matched observed aXa concentrations (Fig. 1), indicating the suitability of the model to be used for the intended purpose in this current study. In addition, the PK model also predicted individual concentration–time profiles well with a sample of two randomly selected subjects, one subject with obesity and one with renal impairment, shown in Figure 2.

Current Study

Model Predictions

Individual aXa concentrations were predicted, using NONMEM, at 30-minute intervals over a 120-hour time period computed using the individual empirical Bayes estimates of the PK parameters. One hundred and twenty hours was chosen because it is the minimum duration of therapy for most thromboembolic diseases. It was also important to predict aXa concentrations beyond 48 hours to

<table>
<thead>
<tr>
<th>TABLE 1. Dose Reduction at 2 Days of Enoxaparin Therapy for Subjects in the Individualized Dosing Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated CL\textsubscript{CR}\textsuperscript{*} (mL/min)</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>50 or greater</td>
</tr>
<tr>
<td>40–49</td>
</tr>
<tr>
<td>30–39</td>
</tr>
<tr>
<td>20–29</td>
</tr>
<tr>
<td>10–19</td>
</tr>
</tbody>
</table>

\textsuperscript{*}Creatinine clearance (CL\textsubscript{CR}) calculated using ideal body weight (IBW) as the body size descriptor in the Cockcroft-Gault equation. Note: a new measure of lean body weight is available that supersedes IBW. Adapted from Barras et al.

FIGURE 1. Observed versus individual model predicted anti-Xa concentrations for the pharmacokinetic model used to generate the individual predicted antiactivated Factor X concentrations. Dots represent data points; solid line represents the unity line and dashed line represents the smooth line.
evaluate the effect of the dose reduction seen in the individualized arm (Table 1) and ensure steady-state data were included in the analysis. The exact dosing history from the RCT was used to predict aXa concentrations. However, if therapy was discontinued in subjects with renal impairment, the dose reduction was applied to the prediction. Individual subject concentration–time profiles were generated and the proportion of time spent within, above, and below the therapeutic range (0.5–1.0 IU/mL) was calculated for each subject.

Evaluation of Predicted Data

The individualized dosing arm was compared with the conventional arm using two methods.

In Method 1, the median proportion of time subjects were therapeutic, supra-, and subtherapeutic were compared over each 24-hour dosing period to allow comparison before and after dose adjustment in the renally impaired subjects. Method 2 focused on subjects with obesity and renal impairment because a dose adjustment occurred in these populations. It should be noted that supra- and subtherapeutic results are negatively correlated with subjects in the supratherapeutic range having a corresponding reduction in the subtherapeutic range.

Statistical Analysis

For Method 1, a Mann-Whitney U test was used to determine statistical significance \( P < 0.05 \) between dosing arms. In Method 2, the median proportion of time within the therapeutic, supratherapeutic, and subtherapeutic range was determined and plotted against time (days) for both dosing arms.

The calculation of time within the different ranges and all statistical analyses were performed using NCSS (2001; Number Cruncher Statistical Systems, Kaysville, UT) software. All graphical analyses were performed using PRISM (GraphPad Prism Version 5.00 for Windows, 2007; GraphPad Software, San Diego, CA).

RESULTS

A total of 240 individual predicted aXa concentrations per subject was generated.

Comparison of Dosing Arms

Method 1

Time Within the Therapeutic Range (0.5–1.0 IU/mL)

When compared with conventional dosing, subjects with renal impairment in the individualized dosing arm achieved a significantly greater proportion of time in the therapeutic range (median [range] = 69.9% [11.3%–91.8%] versus 42.6% [13.9%–71.4%], \( P = 0.02 \)). Obese subjects in the individualized arm had a greater but nonsignificant difference in the proportion of time within the therapeutic range (median [range] = 65.4% [34.3%–81.4%] versus 58.2% [0%–78.4%], \( P = 0.27 \)). When combined, all subjects in the individualized arm had a greater but nonsignificant difference in the proportion of time within the therapeutic range (median [range] = 58.2% [0%–88.7%] versus 56.8% [9.1%–98.8%], \( P = 0.28 \)) (Table 2).

Supratherapeutic (greater than 1.0 IU/mL)

Subjects with renal impairment in the individualized dosing arm had a significantly smaller proportion of time in the supratherapeutic range when compared with the conventional arm (median [range] = 9.3% [0%–67.0%] versus 37.1% [0%–85.7%], \( P = 0.02 \)), suggesting that conventionally dosed subjects received doses that were too big. There was no significant difference in the proportion of time in the supratherapeutic range between the two dosing arms for obese and all subjects (Table 2).
TABLE 2. Median (range) Proportion of Predicted Time Within Therapeutic (0.5–1.0 IU/mL), Supratherapeutic (Greater Than 1.0 IU/mL), and Subtherapeutic (Less Than 0.5 IU/mL) Range for Each Subject Population*

<table>
<thead>
<tr>
<th>Subject Population</th>
<th>Individualized Arm</th>
<th>Conventional Arm</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal impairment†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapeutic</td>
<td>69.9 (11.3–91.8)</td>
<td>42.6 (13.9–71.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>Supratherapeutic</td>
<td>9.3 (0–67.0)</td>
<td>37.1 (0–85.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Subtherapeutic</td>
<td>12.9 (0.4–80.7)</td>
<td>15.7 (0.4–51.1)</td>
<td>0.97</td>
</tr>
<tr>
<td>Obesity‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapeutic</td>
<td>65.4 (34.3–81.3)</td>
<td>58.2 (0–78.4)</td>
<td>0.27</td>
</tr>
<tr>
<td>Supratherapeutic</td>
<td>10.4 (0–68.4)</td>
<td>0 (0–60.6)</td>
<td>0.44</td>
</tr>
<tr>
<td>Subtherapeutic</td>
<td>12.2 (1.3–24.2)</td>
<td>24.0 (0.9–100)</td>
<td>0.46</td>
</tr>
<tr>
<td>All subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapeutic</td>
<td>58.4 (0–88.7)</td>
<td>56.8 (9.1–91.8)</td>
<td>0.28</td>
</tr>
<tr>
<td>Supratherapeutic</td>
<td>14.1 (0–85.3)</td>
<td>21.6 (0–94.8)</td>
<td>0.9</td>
</tr>
<tr>
<td>Subtherapeutic</td>
<td>15.8 (0.4–90.9)</td>
<td>11.7 (0.4–100)</td>
<td>0.63</td>
</tr>
</tbody>
</table>

*Individual subject concentration–time profiles were predicted and the proportion of time spent within, above, and below the therapeutic range (0.5–1.0 IU/mL) was calculated for each subject.
†Renal impairment is defined as a creatinine clearance less than 50 mL/min using ideal body weight as the body size descriptor in the Cockcroft-Gault equation.‡ Obesity is defined as total body weight 100 kg or greater.

**Subtherapeutic (less than 0.5 IU/mL)**

There was no significant difference in the proportion of time within the subtherapeutic range between the dosing arms for all obese and renally impaired subjects (Table 2). Of note was that obese subjects in the conventional arm had 24% of the time below the therapeutic range compared with 12.2% of the time for the individualized arm. This difference was most likely the result of empiric dose reductions such as dose capping, discussed further subsequently.

**Method 2**

Plots of the median proportion of time within, above, and below the therapeutic range over the 5-day dosing period are shown for subjects with renal impairment (Fig. 3A–C) and obesity (Fig. 4A–C).

**Subjects With Renal Impairment**

Subjects with renal impairment who received individualized dosing had a greater proportion of time within the therapeutic range when compared with conventional dosing over all 5 days (Fig. 3A). The greatest disparity between dosing arms was observed after 48 hours, when subjects in the conventional arm had a greater proportion of time in the supratherapeutic range compared with the individualized arm (Fig. 3B). Subjects in the conventional arm had a higher proportion of time in the subtherapeutic range during the first 72 hours (Fig. 3C), but after this time, subjects in the individualized arm had a greater proportion of time below the therapeutic range.

**Subjects With Obesity**

Subjects with obesity who were dose-individualized had a greater proportion of time in the therapeutic range over the 5 days (Fig. 4A). Obese subjects in the conventional arm had a smaller proportion of time in the supratherapeutic range after 48 hours (Fig. 4B); this was the result of a consistently greater proportion of time in the subtherapeutic range (Fig. 4C).

**DISCUSSION**

A therapeutic range for enoxaparin aXa concentrations of 0.5 to 1.0 IU/mL was suggested following results of the TIMI 11A study. A recent RCT demonstrated that individualized dosing of enoxaparin for subjects with renal impairment and/or obesity resulted in a significant reduction in bleeding when compared with conventional dosing. During this RCT, aXa concentrations were collected, but no comparison of the two dosing groups using these observed concentrations was presented given the sparse sampling design. In the current study, we have demonstrated that the individualized dosing arm was superior to conventional dosing at achieving and maintaining a therapeutic range in subjects with renal impairment, which further supports the benefits of dose individualization for enoxaparin in contemporary pharmacotherapeutics.

Current dosing strategies can broadly be divided into two methods: fixed/flat dosing and individualized therapy. A fixed-dose strategy, in which all subjects receive the same dose, is simple to use, but it does not consider the variability in the dose-exposure–response relationship that can exist between subjects. Dose individualization strategies generally use one or more methods: dosing based on a covariate such as the subject’s weight (milligrams per kilogram); empiric/protocol based dosing to a desired response such as an international normalized ratio for warfarin; and dosing aimed at a therapeutic range to optimize clinical outcomes. Fixed dosing is hopefully being replaced by individualized strategies aimed at maximizing the effectiveness of a drug and minimizing adverse events, hence optimizing patient care. Two recent studies have demonstrated the benefits of covariate-based dosing by showing that fixed dosing will only result in approximately 35% of subjects within the therapeutic range, whereas covariate based dosing will achieve 60% to 70%.

At present, conventional dosing of enoxaparin does have a covariate based dose structure that includes renal function and weight (TBW). Despite this, three issues arise...
FIGURE 3. Median proportion of time in the therapeutic, supratherapeutic, and subtherapeutic range for subjects with a creatine clearance less than 50 mL/min (circle/dash = conventional dosing, triangle/bold line = individualized dosing). (A) Therapeutic range (0.5–1.0 IU/mL). (B) Supratherapeutic range (greater than 1.0 IU/mL). (C) Subtherapeutic range (less than 0.5 IU/mL).

FIGURE 4. Median proportion of time in the therapeutic, supratherapeutic, and subtherapeutic range for subjects with a total body weight 100 kg or greater (circle/dash = conventional dosing, triangle/bold line = individualized dosing). (A) Therapeutic range (0.5–1.0 IU/mL). (B) Supratherapeutic range (greater than 1.0 IU/mL). (C) Subtherapeutic range (less than 0.5 IU/mL).
that diminish the ability of conventional dosing to achieve and maintain concentrations in the therapeutic range.

First, conventional dosing dichotomizes renal function, a continuous variable, at a value of $CL_{\text{cr}}$ of 30 mL/min, at which point the dose is arbitrarily reduced by either 33% or 50%. It is illogical to assume the CL of a drug will halve at a point value of renal function. In contrast, the individualized strategy comprises a four-dose load (48 hours) to achieve therapeutic concentrations followed by a linear dose reduction to maintain the therapeutic range (Table 1). The linear dose reduction, based on renal function, is an appropriate physiological approach to dosing enoxaparin in subjects with renal impairment. The importance of the linear dose reduction has been demonstrated in this study because the proportion of time in the supratherapeutic range in the conventional arm is approximately four times that of the individualized arm (37.1% versus 9.3%; Table 2). In particular, this difference occurs after 48 hours (Fig. 3B). Because $\alpha$Xa concentrations greater than 1.0 IU/mL increase the risk of bleeding events, subjects with renal impairment that are conventionally dosed are at a greater risk of an adverse outcome beyond this time.

Second, conventional dosing uses TBW as the body size descriptor for dose calculation. Han et al demonstrated recently that LBW is a more scientifically robust metric compared with TBW for predicting drug CL in subjects of varying body compositions, in particular the obese. More importantly, LBW has been shown to be the best body size descriptor to describe enoxaparin CL in two population PK studies. Because muscle mass is correlated with 99% of all metabolic processes, dosing regimens adjusted by LBW rather than TBW will result in comparable $\alpha$Xa exposure across a diverse range of body compositions. LBW (equations 2 and 3) is the body size descriptor of choice in obese subjects (TBW 100 kg or greater) for dosing enoxaparin at a dose of 1.5 mg/kg (LBW) twice a day.

$$LBW\text{ (male)} = \frac{9270 \times Wt}{6680 + 216 \times BMI} \quad (\text{Equation 2})$$

$$LBW\text{ (female)} = \frac{9270 \times Wt}{8780 + 244 \times BMI} \quad (\text{Equation 3})$$

where BMI = body mass index.

What was interesting in this study was that there was no significant difference in the proportion of time within the therapeutic range between dosing arms for obese subjects. This was probably the result of small recruitment numbers; however, “dose capping” may also confound the results. Dose capping of enoxaparin is commonly used in conventional dosing. and the effects are clearly seen in this study, because 24% of time is spent in the subtherapeutic range (Table 2), a result that is consistent over time (Fig. 4C). This is not surprising, because many clinicians recognize the risk of bleeding when obese subjects are dosed based on TBW, although this practice may result in subtherapeutic $\alpha$Xa concentrations and the potential for reinfarction.

Finally, conventional dosing fails to recommend a body size descriptor, representative of endogenous creatinine production, for calculating $CL_{\text{cr}}$. The C-G equation, like other predictive formulae, produce erroneously high estimates of glomerular filtration rate in the obese subject, because excess body mass in the obese is mostly adipose tissue as opposed to muscle. Because creatinine is a byproduct of muscle metabolism, when no adjustment is made for the increase in total body mass such as standardization with LBW, glomerular filtration rate will be routinely overestimated. A small study confirmed this recently by demonstrating that glomerular filtration rate, when normalized using LBW in the C-G formula, was not different between obese and normal weighted subjects.

The results presented in this article are not without limitation. Conventional dosing was dictated by the prescriber; therefore, if therapy was discontinued before 120 hours, the extrapolation of the dose for simulation has the potential to be inaccurate if doses change or if the PK of enoxaparin varies with time. It should be noted, however, that during the RCT, no dose adjustments were seen in subjects in the conventional arm who were on therapy longer than 48 hours, which is indicative that altering the initial dose is unlikely. Similarly, there are no data that we are aware of that quantifies interoccasion variability for enoxaparin, and no studies have been published demonstrating time-dependent PK. Another limitation was the lack of obese subjects recruited. This is indicative of contemporary medical practice, in which clinicians often elect to use other anticoagulants rather than enoxaparin as a result of the perceived risk of bleeding if a dose based on TBW is prescribed. It should be noted that the precise dose strategy from the PL was not used in approximately 40% of subjects in the conventional arm. Therefore, direct comparisons of the individualized dose strategy to the PL could not be reported. However, in a recent international survey of low-molecular-weight heparin use, 96% of hospitals did not adhere to the PL, demonstrating that clinicians are aware of the inadequacies of the PL and that it is seldom used in clinical practice.

Future Dosing Strategies for Enoxaparin

This study has demonstrated that individualized dosing of enoxaparin is superior to conventional dosing in achieving and maintaining concentrations in the therapeutic range, but further individualization is warranted. One method may be to target concentrations using Bayesian methods, which have been advocated for other drugs, for example aminoglycosides. It is estimated that these methods could achieve effective concentrations in 90% of subjects; therefore, this may be the future for enoxaparin dosing.

CONCLUSION

An individualized dosing strategy for enoxaparin is more effective than conventional dosing at achieving and maintaining a therapeutic range in subjects with renal impairment, which could decrease bleeding events and mortality.

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