Thrombosis Research (2005) **116**, 41—50

ELSEVIER

THROMBOSIS RESEARCH

intl.elsevierhealth.com/journals/thre

Regular Article

Dosage of enoxaparin among obese and renal impairment patients☆

Annie Bazinet[a,b], Karine Almanric[a,b], Catherine Brunet[a,b], Isabel Turcotte[a,b], Josée Martineau[a], Stéphanie Caron[a], Normand Blais[a], Lyne Lalonde[a,b,c,d,*]

[a]*Cité de la Santé de Laval, Quebec, Canada*
[b]*Faculty of Pharmacy, University of Montreal, Quebec, Canada*
[c]*Aventis Pharma Endowment Chair in Ambulatory Pharmaceutical Care, Faculty of Pharmacy, University of Montreal, Quebec, Canada*
[d]*Research Team in Primary Care, Cité de la Santé de Laval, Quebec, Canada*

Received 16 June 2004; received in revised form 4 October 2004; accepted 8 October 2004
Available online 6 November 2004

KEYWORDS
Low-molecular-weight heparin;
Impaired renal function;
Obesity;
Anticoagulant;
Anti-Xa activity

Abstract

Background: Enoxaparin dosage for obese patients and patients with renal impairment remains controversial.
Objective: To compare anti-factor Xa activity (anti-Xa) among obese and renal impairment patients to patients with healthy weight and adequate renal function.
Design: Open, prospective, nonrandomized clinical trial.
Setting: A major community teaching hospital.
Patients: A total of 233 patients with prescription of enoxaparin.
Interventions: Enoxaparin 1.5 mg/kg once daily or 1 mg/kg twice daily except those on dialysis, who received 75% of the dose.
Measurements: Anti-Xa was measured 4 h post-injection on day 2 or 3.
Results: Mean (95% confidence interval (95% CI)) anti-Xa was equal to 1.14 IU/mL (1.07—1.21) and 1.14 IU/mL (1.08—1.20) among patients who received one (n=92) and two injections (n=122) per day, respectively. Anti-Xa increases with body mass

Abbreviations: Anti-Xa, anti-factor Xa activity; BMI, body mass index; CrCl, creatinine clearance; LMWH, low-molecular-weight heparins; S.D., standard deviation.

☆ This study was made possible by a grant to the Cité de la Santé de Laval from Aventis Pharma Canada for funding of master's projects in pharmaceutical practices.

* Corresponding author. Research Team in Primary Care, Cité de la Santé de Laval, 1755 René-Laennec Blvd, Room D-S145, Laval, Quebec, Canada H7M 3L9. Tel.: +1 450 668 1010x2743; fax: +1 450 975 5089.
E-mail address: lyne.lalonde@umontreal.ca (L. Lalonde).

0049-3848/$ - see front matter
doi:10.1016/j.thromres.2004.10.004

index (BMI) (0.01 IU/mL for each kg/m^2; 95% CI: 0.002—0.017), but the increase is insufficient to reach supratherapeutic anti-Xa. Anti-Xa decreases with higher creatinine clearance (CrCl) (—0.003 IU/mL for each mL/min; 95% CI: —0.006 to —0.001). On the twice-daily regimen, this is sufficient to reach supratherapeutic anti-Xa. The odd ratio (OR) (95% CI) of having a nontherapeutic anti-Xa is equal to 2.28 (1.25—4.16) when enoxaparin is administered twice daily and to 3.03 (1.16—7.86) among severe renal impairment patients (≤30 mL/min).
Conclusions: Based on Anti-Xa, no dosage adjustments are required in obese patients. In renally impaired patients, adjustments may be necessary when enoxaparin is administered twice daily.

Introduction

Low-molecular-weight heparins (LMWH) have better bioavailability and a more predictable anticoagulant effect than unfractionated heparin [1]. They can be administered subcutaneously and are therefore simpler to use [1,2]. Given that LMWH are comprised of a complex of molecules, some of which are not completely characterized, the pharmacokinetics profile for these drugs is established based on the surrogate marker of their activity, which is their effect against coagulation factor Xa. Pharmacokinetics of LMWH is linear and predictable, however, in obese and renally impaired patients anti-factor Xa activity (anti-Xa) should periodically be monitored [1—3].

Enoxaparin, a LMWH, is primarily eliminated renally. In patients with renal impairment, the elimination half-life is approximately 5.12 h, compared to 2.94 h for young healthy volunteers [4]. Given the risk of drug accumulation, many authors recommend measuring anti-Xa in renally impaired patients [5—8]. However, studies involving this population have yielded contradictory results regarding the need for dosage adjustments and the level of creatinine clearance (CrCl) that would indicate that adjustments are required [4,6,7,9,10]. Few studies, moreover, make specific adjustment recommendations [1,7,10—14].

Enoxaparin treatment doses are calculated in terms of actual patient weight, but, because the drug is not distributed in fat, there is a possibility of excessive drug exposure in obese patients. The manufacturer therefore recommends a maximum single-injection dose of 18,000 IU (180 mg) to treat deep-vein thrombosis with or without pulmonary embolism and a 12-h dose of no more than 10,000 IU (100 mg) to treat unstable angina and non-Q-wave myocardial infarction [5]. So far, few studies have been conducted on obese patients and they are inconclusive on the issue of dosage adjustment [1,11,15,16].

Although it is recommended to measure anti-Xa in obese and renally impaired patients, the definition of therapeutic ranges of anti-Xa has not been validated [6,17]. Few studies have suggested that anti-Xa is inversely related to thrombotic events [2,18,19], however, the minimum level of activity required for treatment to be effective has not been well defined [6,17]. Moreover, data from clinical trials in which anti-Xa has been measured do not establish a link between anti-Xa, bleeding and the effect of the drug [20]. However, the literature does note that bleeding is more frequent when anti-Xa levels are greater than 0.8—1.0 IU/mL at steady state [2,17]. Given the lack of clinical data allowing us to establish efficacy and safety thresholds, the target levels of anti-Xa are based primarily on the consensus of experts [21] and founded principally on pharmacokinetic parameters [18,22—26]. Hitherto, studies have only very rarely reported anti-Xa levels [21].

To better understand how anti-Xa fluctuates as a function of patient weight and CrCl, we conducted a prospective clinical trial to compare anti-Xa levels after 2 to 3 days of treatment in obese, low-weight, and renally impaired patients as compared to patients with healthy weight and adequate renal function.

Method

Research design

An open, prospective, nonrandomized clinical trial was conducted between October 16, 2002 and May 9, 2003 at the Cité de la Santé de Laval hospital. The project was approved by the hospital's research ethics board.

Patients who were hospitalized or admitted to emergency and were prescribed enoxaparin were identified every day from the pharmacy database.

Patients were also referred by the anticoagulation, nephrology and day clinics.

Study population

To be included, patients had to: (1) receive a new prescription of enoxaparin; (2) have an expected duration of enoxaparin treatment of 48 h or more; (3) be 18 or older; (4) speak French or English or have an interpreter; (5) be able to give informed consent; and (6) agree to participate in the study. Originally, the expected treatment duration was 5 days and more but was changed to 48 h and more during the study.

We applied the following exclusion criteria: (1) enoxaparin dosage different from that specified in the protocol; (2) having received enoxaparin or another LMWH in the previous 40 h; (3) participation in another study; (4) pregnancy; (5) antithrombin III deficiency; (6) an international normalized ratio over 2.0; (7) receiving a GP IIb/IIIa receptor antagonist or a thrombolytic agent; (8) having received an intravenous bolus of enoxaparin; and (9) a contraindication to using enoxaparin.

Enoxaparin

The initial dose of enoxaparin was 1.5 mg/kg once daily or 1 mg/kg twice daily rounded to the nearest 5 mg. No maximum dose was set for obese patients. Participants on dialysis were given 75% of the other subjects' recommended initial dosage, that is, 1.125 mg/kg once daily or 0.75 mg/kg twice daily.

Anti-Xa activity

Anti-Xa was measured at its peak, 4 h after administration of enoxaparin [2,5,17]. This is the ideal time for an assay, as opposed to the trough, since it provides the best reflection of the pharmacokinetic exposure to LMWH [11,17]. It is estimated it takes seven half-lives ($t_{1/2}$) to reach steady state, namely 35 h for renally impaired patients ($t_{1/2}$=5.12 h) and 21 h for others ($t_{1/2}$=2.94 h) [5]. For patients on twice-daily doses, anti-Xa were measured 4 h after the third, fourth or fifth enoxaparin dose. For patients on once-daily treatment, the measurement was made 4 h after the second or third dose.

Blood samples were taken in glass tubes containing 0.5 mL of 3.2% sodium citrate, centrifuged at 3500 RPM at 10 °C for two consecutive 15-min cycles and frozen at an average temperature of −75 °C until sent to the laboratory on dry ice. All anti-Xa analyses were conducted in one laboratory with a chromogenic technique using the STA® Rotachrom Heparin kit from Diagnostica.

Bleeding

Five days after the start of treatment, bleeding episodes were documented for all subjects. Those who had been discharged were telephoned by one of the investigators (KA, AB, CB, IT). For those still in hospital, documentation was based on the medical record or an interview with the patient. To classify bleeding severity, a modified version of the Warfarin Optimized Outpatient Follow-up Study Classification was used [27]. According to this classification, "minor" bleeding has no or little clinical significance, is associated with no cost and does not require medical evaluation. In contrast, "significant" bleeding requires medical evaluation or is associated with at least a 3% reduction in hematocrit, or more than 12 g/L (1.2 g/dL) reduction in the hemoglobin level. "Major" bleeding requires hospitalisation and transfusions. "Life threatening" bleeding is associated with cardiopulmonary arrest, surgical or angiographic intervention or irreversible sequelae and "fatal" bleeding is directly related to death.

Patient characteristics

Measurements of patient weight, height and serum creatinine were requested. A serum creatinine was requested at entrance into the study unless serum creatinine was measured within 7 days and documented in the hospital chart. Patients were measured and weighted by a nurse unless they were able to precisely report their height and weight (measured in the last 2 weeks). The Cockcroft and Gault formula was used to calculate CrCl [28—31].

The following factors that may affect bleeding risk were documented: taking warfarin, nonsteroidal anti-inflammatories, aspirin, ticlopidine, or clopidogrel; a history of gastrointestinal bleeding; age; and comorbidities. Each patient initial bleeding risk was estimated using the Outpatient Bleeding Risk Index [32,33]. This index classifies patients in three risk categories based on their number of independent risk factors: (1) age over 65 years; (2) history of stroke; (3) history of gastrointestinal bleeding; (4) recent myocardial infarction, hematocrit<30%, serum creatinine>132 μmol/L (1.5 mg/dL) or diabetes mellitus. Low risk patients have no risk factors, intermediate-risk patients have one or two risk factors and high-risk patients have three or four risk factors.

Statistical analyses

Mean anti-Xa levels (95% CI) were calculated for the once- and twice-daily regimens for participant subgroups categorized by body mass index (BMI) (low weight: BMI<18 kg/m^2; healthy weight: BMI≥18 and ≤30 kg/m^2; obese: BMI>30 kg/m^2) and renal function (adequate renal function: CrCl>50 mL/min; moderate renal impairment: CrCl≤50 and >30 mL/min; severe renal impairment: ≤30 and >10 mL/min; and dialysis patients). We also calculated the number and proportion of subjects reaching subtherapeutic, therapeutic and supratherapeutic anti-Xa levels. As suggested by the American Pathologists Conference XXXI on laboratory monitoring of anticoagulant therapy, the definition of therapeutic activity differed depending on the drug regimen: once daily: 1.00—2.00 IU/mL, twice daily: 0.5—1.1 IU/mL [21]. This is consistent with the recommendations of the Consensus Conference on Antithrombotic Therapy suggesting a target range of 1.0—2.0 and 0.6—1.0 IU/mL, for once-daily and twice-daily administration, respectively, for patients with morbid obesity and renal failure [2].

We assessed the distribution of the variables to evaluate if they were normally distributed and to identify outliers. Univariate regression models were used to calculate variation in anti-Xa by patient BMI, CrCl, age and gender. Dialysis patients, who received lower doses, were not included. The regression coefficients for BMI (p=0.036), CrCl (p<0.001) and gender (p=0.001) were statistically different from zero; those for drug regimen (p=0.919) and age (p=0.07) were not. Hierarchical linear models were constructed to describe the anti-Xa level as a function of BMI, CrCl, gender and age. The final model included the following variables: age, gender, BMI and CrCl. This model was applied separately to patients on once- and twice-daily treatment. However, since the 95% CI of the regression coefficients of BMI and CrCl overlapped in the models, only the results of the regression model combining both regimens are reported.

Finally, we used a logistic regression model to estimate the odds ratio for achieving nontherapeutic results and the associated 95% CI. Dialysis patients were excluded. All variables of interest (age, gender, BMI, CrCl and drug regimen) were included. Dummy variables were created for CrCl (moderate and severe renal impairment versus adequate renal function) and BMI (obese versus patients with low-weight and healthy weight).

Results

During the recruitment period, 1600 patients were prescribed enoxaparin. Of these, 523 receiving a therapeutic dose were asked to participate in the study; 259 were ineligible, and 31 refused. The ineligible patients were excluded for one or more of the following reasons: enoxaparin dosage different from protocol specifications (n=71); treatment duration too short (n=117); aged under 18 (n=1); not speaking French or English and having no interpreter (n=3); unable to give informed consent (n=42); treatment with enoxaparin or another LMWH in the preceding 40 h (n=40); participation in another study (n=2), pregnancy (n=2); antithrombin III deficiency (n=1); therapeutic international normalized ratio (n=3); contraindication to enoxaparin use (n=1). In all, 233 patients were enrolled.

As Table 1 shows, the primary treatment indications included atrial fibrillation, myocardial infarction, unstable angina, deep vein thrombosis and pulmonary embolism. Almost half the patients were receiving concomitant treatment with warfarin and/or acetylsalicylic acid. The patient's treating physician was responsible for prescribing warfarin

Table 1 Characteristics of study population

Number of participants: *N*	233
Gender: *N* (%)	
Male	132 (56.7%)
Female	101 (43.3%)
Age (years): mean (±S.D.)	66.6 (±13.3)
Weight (kg): mean (±S.D.)	78.0 (±20.1)
Height (cm): mean (±S.D.)	164.9 (±10.2)
Initial dosage: *N* (%)	
Once daily	101 (43.3%)
Twice daily	132 (56.7%)
Treatment indications[a]: *N* (%)	
Atrial fibrillation	78 (33.5%)
Myocardial infarction	53 (22.7%)
Unstable angina	48 (20.6%)
De novo deep vein thrombosis	26 (11.2%)
De novo pulmonary embolism	17 (7.3%)
Other indications	55 (23.6%)
Concomitant medication that may affect bleeding risk[b]: *N* (%)	
Warfarin	114 (48.4%)
Acetylsalicylic acid	113 (48.5%)
Clopidogrel	42 (18.6%)
Nonsteroidal anti-inflammatories	15 (6.4%)
Initial bleeding risk[c]: *N* (%)	
Low	49 (21.1%)
Moderate	175 (75.1%)
High	9 (3.9%)

[a] Some patients had more than one treatment indication.
[b] Some patients took more than one medication that may affect bleeding risk.
[c] Estimated with the Bleeding Risk Index [32,33].

and acetylsalicylic acid when indicated. A majority (n=175) had a moderate bleeding risk.

Nineteen of the 233 patients enrolled discontinued their treatment before the first anti-Xa assay, leaving 214 to be tested. On average, blood samples were taken 4.04 h (standard deviation (S.D.): 0.51 h) after enoxaparin was administered and after a mean of 33.3 h (S.D.: 9.9 h) of treatment. Anti-Xa did not vary with number of hours of treatment (p=0.74), suggesting it was measured at steady state.

As described earlier, anti-Xa was measured at its peak concentration (4 h after administration of enoxaparin) after the third, fourth or fifth dose for patients on twice-daily regimen and after second or third dose for patients on once-daily regimen. Mean anti-Xa (95% CI) was 1.14 IU/mL (1.07—1.21) with a standard deviation of 0.30 IU/mL for subjects on once-daily therapy (n=92) and 1.14 IU/mL (1.08—1.20) with a standard deviation of 0.34 IU/mL for patients on twice-daily treatment (n=122). For patients on once-daily treatment, 39% of measured levels were subtherapeutic (n=36), 59% therapeutic (n=54) and 2% supratherapeutic (n=2). For patients on twice-daily treatment, 3% were subtherapeutic (n=3), 45% therapeutic (n=55) and 53% supratherapeutic (n=64). The results indicate that the once- and twice-daily regimens produce similar anti-Xa levels. Since target levels differ for each regimen, however, when enoxaparin is injected once daily, a large proportion of results (39%) are subtherapeutic, and, when it is administered twice daily, a majority (53%) are supratherapeutic.

Table 2 indicates that, on once-daily therapy, mean anti-Xa (95% CI) was 1.13 IU/mL (1.04—1.22) for healthy-weight participants (BMI≥18 and ≤30 kg/m^2) and 1.15 IU/mL (1.02—1.28) for obese ones (BMI>30 kg/m^2). Similar results were observed among patients on twice-daily treatment: healthy weight: 1.12 IU/mL (1.03—1.20); obese: 1.17 IU/mL (1.08—1.25). Only two low-weight patients (BMI<18 kg/m^2) were recruited. The proportion of patients on the once-daily regimen with results in the therapeutic range is 58% for healthy-weight patients and 60% for obese ones. The corresponding proportions for the twice-daily regimen are 46% and 45%, respectively. The bivariate analyses thus suggest that anti-Xa does not vary as a function of BMI.

Table 3 shows that, on the once-daily regimen, mean anti-Xa (95% CI) is 1.21 IU/mL (1.09—1.33) for moderately (CrCl≤50 and >30 mL/min) and 1.18 IU/mL (0.92—1.44) for severely (≤30 and >10 mL/min) renally impaired patients, but 1.10 IU/mL (1.00—1.20) for subjects with adequate (CrCl>50 mL/min) renal function. The overlapping confidence intervals indicate that there is no statistically significant difference between patients categorized by renal function. The proportion of moderately and severely renally impaired patients not on dialysis who reached target therapeutic ranges was equal to 78% and 64%, respectively. Only 2 of 13 dialysis patients achieved therapeutic levels.

On the twice-daily regimen, mean anti-Xa (95% CI) is higher for patients with moderate (1.25 IU/mL (1.12—1.39)) and severe renal impairment (1.27 IU/mL (1.15—1.40)) than for subjects with adequate kidney function (1.06 IU/mL (0.99—1.14)). Dialysis patients, taking the 75% dose, achieved a mean level of 1.03 IU/mL (0.45—1.61),

Table 2 Anti-Xa activity measured 4 h post-dose on day 2 or 3 of treatment by body mass index

	Weight range:		Anti-Xa activity (IU/mL): mean (95% CI)	Number of patients (%)		
	N	(kg) min—max		Subtherapeutic	Therapeutic	Supratherapeutic
Once-daily administration				*<1.00 IU/mL*	*1.00—2.00 IU/mL*	*>2.00 IU/mL*
Body mass index						
Low weight: <18 kg/m^2	0	—	NA	NA	NA	NA
Healthy weight: ≥18 and ≤30 kg/m^2	62	40—103	1.13 (1.04—1.22)	25 (40%)	36 (58%)	1 (2%)
Obese: >30 kg/m^2	30	66—136	1.15 (1.02—1.28)	11 (37%)	18 (60%)	1 (3%)
Twice-daily administration				*<0.5 IU/mL*	*0.5—1.1 IU/mL*	*>1.1 IU/mL*
Body mass index						
Low weight: <18 kg/m^2	2	40—42	1.40 (−0.45—3.24)	0 (0%)	0 (0%)	2 (100%)
Healthy weight: ≥18 and ≤30 kg/m^2	69	45—95	1.12 (1.03—1.20)	2 (3%)	32 (46%)	35 (51%)
Obese: >30 kg/m^2	51	63—159	1.17 (1.08—1.25)	1 (2%)	23 (45%)	27 (53%)

Table 3 Anti-Xa activity measured 4 h post-dose on day 2 or 3 of treatment by creatinine clearance

	N	Anti-Xa activity (IU/mL): mean (95% CI)	Number of patients (%)		
			Subtherapeutic	Therapeutic	Supratherapeutic
Once-daily administration			*<1.00 IU/mL*	*1.00–2.00 IU/mL*	*>2.00 IU/mL*
Creatinine clearance					
Adequate renal function: >50 mL/min	38	1.10 (1.00–1.20)	16 (42%)	22 (58%)	0 (0%)
Moderate renal impairment: >30 and ≤50 mL/min	27	1.21 (1.09–1.33)	5 (19%)	21 (78%)	1 (4%)
Severe renal impairment: ≤30 and >10 mL/min	14	1.18 (0.92–1.44)	5 (36%)	9 (64%)	0 (0%)
Dialysis patients	13	1.04 (0.79–1.30)	10 (77%)	2 (15%)	1 (8%)
Twice-daily administration			*<0.5 IU/mL*	*0.5–1.1 IU/mL*	*>1.1 IU/mL*
Creatinine clearance					
Adequate renal function: >50 mL/min	68	1.06 (0.99–1.14)	2 (3%)	39 (57%)	27 (40%)
Moderate renal impairment: >30 and ≤50 mL/min	27	1.25 (1.12–1.39)	0 (0%)	10 (37%)	17 (63%)
Severe renal impairment: ≤30 and >10 mL/min	22	1.27 (1.15–1.40)	0 (0%)	5 (23%)	17 (77%)
Dialysis patients	5	1.03 (0.45–1.61)	1 (20%)	1 (20%)	3 (60%)

a result similar to that for patients with adequate renal function. The proportion of patients achieving therapeutic anti-Xa decreases as a function of CrCl; it is 57% for patients with adequate renal function, 37% for moderately renally impaired patients and 23% for severely impaired ones. The bivariate analyses thus suggest the twice-daily regimen produces higher mean anti-Xa levels for moderately and severely renally impaired patients than for those with adequate renal function.

As Fig. 1 illustrates, anti-Xa decreases on average 0.003 IU/mL for each 1-mL/min increase in CrCl (95% CI: −0.006 to −0.001) after adjusting for age, gender and BMI. In the same way, the adjusted anti-Xa increases 0.01 IU/mL for every increase of 1 kg/m^2 (95% CI: 0.002–0.017).

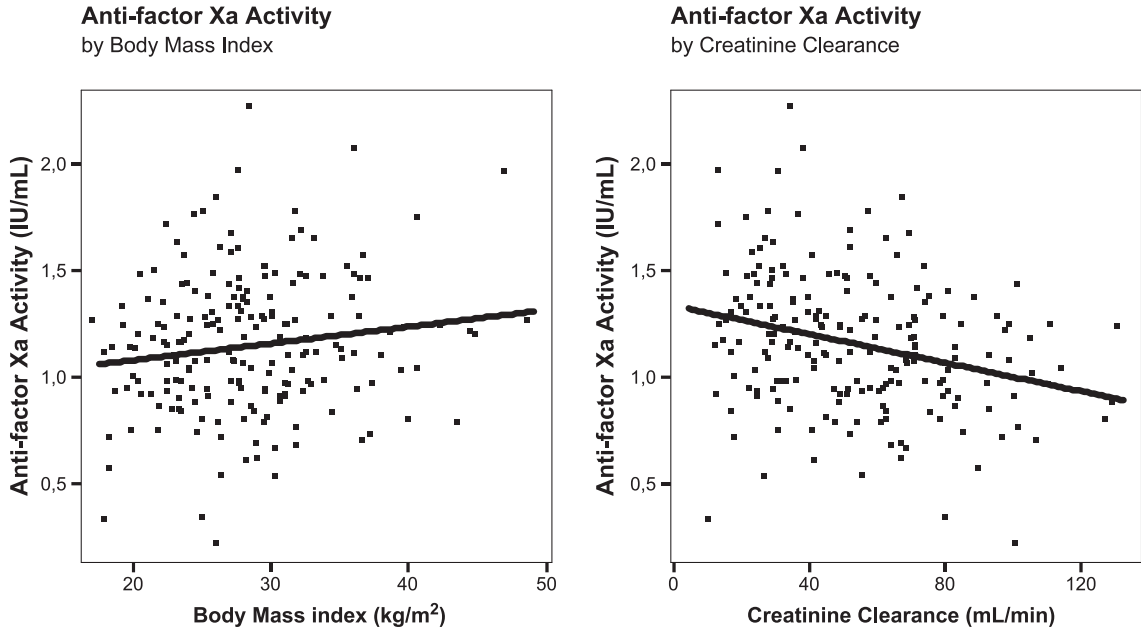

Figure 1 Anti-factor Xa activity among all participants except those on dialysis as a function of patient body mass index and creatinine clearance among participants who received enoxaparin once and twice a day (*n*=196). The univariate regression line represents the estimated mean change in anti-factor Xa activity as a function of body mass index and creatinine clearance.

Table 4 Multivariate logistic regression model to identify variables that may affect achievement of target therapeutic ranges for anti-Xa activity among non-dialysis patients who received enoxaparin once or twice daily

Variables	Odds ratio	(95% CI)
Body mass index (kg/m^2) (overweight versus normal weight)	0.95	(0.521—1.73)
Renal impairment		
Moderate impairment versus normal renal function	1.16	(0.54—2.51)
Severe impairment versus normal renal function	3.03	(1.16—7.86)
Regimen		
Twice daily versus once daily	2.28	(1.25—4.16)
Age (years)	1.02	(0.99—1.05)
Gender		
Male versus female	0.88	(0.47—1.67)

Table 4 shows that the twice-daily regimen is associated with a higher risk of obtaining a non-therapeutic activity level than the once-daily regimen (odds ratio (95% CI): 2.28 (1.25—4.16)). Patients with severe renal impairment are also at higher risk of having a nontherapeutic activity level (odds ratio (95% CI): 3.03 (1.16—7.86)).

In all, 25 (10.7%) patients presented with a bleeding episode during the first 5 days of treatment: 2 minor, 20 significant and 3 major. For 17 (85%) of those with significant bleeding, it was considered significant because of a decrease in hematocrit of over 3%, and all 20 (100%) had at least a 12 g/L (1.2 g/dL) decrease in haemoglobin but no clinically important bleeding. There was no difference in mean (±S.D.) anti-Xa between patients who had a bleeding episode and those who did not (1.13±0.32 versus 1.14±0.33). Subjects on twice-daily treatment accounted for 48% (n=12) of patients with a bleeding episode. In all, the initial bleeding risk was low for 20% (n=5), moderate for 76% (n=19) and high for 4% (n=1).

Discussion

Monitoring of anti-Xa activity is recommended for patients with morbid obesity or renal failure [1,2,6,7,17]. Although therapeutic ranges have not been clinically validated, target ranges, at peak concentration, have been defined by a consensus of expert practitioners and varies according to the frequency of administration. The suggested ranges are 0.6—1.0 IU/mL [2] or 0.5—1.1 UI/mL [21] for a twice-daily regimen, and 1.0—2.0 IU/mL [2] for a once-daily regimen. In this study, enoxaparin was administered once daily at a dose of 1.5 mg/kg or twice daily at a dose of 1.0 mg/kg. For patients on dialysis, the dosage of enoxaparin was reduced by 25%. Anti-Xa was measured at peak concentration (4 h post-dose), 2 or 3 days after the initiation of treatment. Surprisingly, both regimens resulted in the same mean (±S.D.) anti-Xa activity (1.14 IU/mL±0.3). However, since they entail different target levels, the twice-daily regimen tends to be associated with supratherapeutic levels, while the once-daily regimen tends to produce subtherapeutic levels, even for patients with healthy weight and adequate renal function.

Our findings clearly indicate that BMI does not significantly influence anti-Xa levels. Indeed, a substantial 10-kg/m^2 difference is associated with no more than a 0.1-IU/mL increase in anti-Xa activity. However, renal function does affect anti-Xa levels. Renally impaired patients who received a full dose of enoxaparin reached higher levels of anti-Xa than patients with adequate renal function, especially on the twice-daily regimen. The multivariate analyses suggest that activity levels increase by 0.03 IU/mL for every 10-mL/min decrease in CrCl. This may lead to supratherapeutic level. For example, a 50-mL/min difference is associated with a 0.15-IU/mL increase in anti-Xa activity. Considering that the average level of anti-Xa is 1.14 IU/mL for both regimens, a 0.15-IU/mL increase would be enough to result in a supratherapeutic level on twice-daily therapy, though it would not be critical on once-daily treatment.

These findings are in accordance with earlier reports. High variability among patients in anti-Xa activity levels has been reported by others [3,12,16,23,24]. Earlier studies of obese subjects also found that anti-Xa levels do not vary according to BMI [10,16,34]. For patients with reduced renal function, others have found that the half-life of enoxaparin increases and elimination decreases [6—12,14]. However, there is no consensus regarding a level for CrCl, below which there is significant risk of accumulation [6]. Thus, while some data point to a risk from 50 mL/min [7,35], others set the level at 30 mL/min [10], while some studies show no accumulation with reduced renal function [10,13,36]. There are a number of possible explanations for these findings: too few subjects [10,13,14], few participants with CrCl<30 mL/min [9,10,13,14]; or results based on a single dose of LMWH [13,14,35]. Our findings indicate that, when CrCl is under 50 mL/min, there is a significant risk of accumulation, particularly for patients on a twice-daily regimen.

There is no strong consensus regarding the need to monitor anti-Xa activity with LMWH [17,37]. The

definition of therapeutic anti-Xa ranges is based on the recommendations of the American Pathologists Conference XXXI on laboratory monitoring of anticoagulant therapy [21]. As stated before, these ranges have not been validated in clinical trials. There are, therefore, no clear indications that supratherapeutic levels are associated with increase risk of bleeding and that subtherapeutic levels are associated with increase risk of thrombosis. It is worth to underline that in our study about 50% of patients with healthy weight and normal renal function did not reach anti-Xa levels considered as "therapeutic". Should everybody be monitored then? Results of large randomised, controlled trials [24,38—40] suggest that compared to unfractionated heparin, unadjusted-dose LMWH, including enoxaparin, are at least as effective and are not associated with increased risk of major bleeding. Anti-Xa activity was not reported in these trials. However, based on the results of our study, we may assume that about half of these patients on Enoxaprin would have had non-therapeutic anti-Xa levels. Considering that enoxaparin is effective and safe despite the fact that 50% of patients are probably not within anti-Xa therapeutic range, we may conclude that anti-Xa monitoring is not required. Our results suggest, however, that among renally impaired patients, especially those on a twice-daily regimen, it may be safer to monitor anti-Xa or to use alternative treatment such as unfractionated heparin [41].

Since February 2003, the manufacturer has recommended reducing the prophylactic and treatment dose of enoxaparin for patients with severe renal impairment (CrCl≤30 mL/min) by 50% [4] on the basis of pharmacokinetic studies and internal company data that demonstrate that, in such cases, accumulation occurs and drug half-life increases by approximately 97% [10,12]. In our study, based on anti-Xa activity, once-daily administration of a full dose of enoxaparin did not result in accumulation among patients with a CrCl≤30 mL/min. In fact, no patients with CrCl≤30 mL/min who were not on dialysis achieved supratherapeutic levels and barely 4% of patients with CrCl between 30 and 50 mL/min did; in contrast a majority (69%) of renally impaired patients on the twice-daily regimen did. Finally, for dialysis patients, who received 75% of the initial dose, average anti-Xa levels were not statistically different from those for patients with a CrCl over 50 mL/min. However, there was only a small number of dialysis patients in the study (n=18). Our results thus indicate that over half of severely or moderately renally impaired patients would achieve therapeutic levels on a once-daily regimen, a result comparable to that observed in patients with adequate renal function. Twice-daily administration of enoxaparin, however, gives rise to supratherapeutic levels in over 50% of cases; the twice-daily dose may therefore need to be reduced.

Our findings are based on the results of a large-scale (n=233) clinical trial, which included patients with healthy weight and adequate renal function. Up to now, few studies have had such a comparison group [8,10,14]. In fact, most available pharmacokinetics data in special populations come from studies with few subjects and no comparison group [10,13—16]. The large number of subjects in our study allowed us to carry out multivariate analyses to confirm observations based on univariate analyses. Furthermore, the rigour of the prospective experimental design enabled us to ensure that all participants received enoxaparin in accordance with the study protocol and that the anti-Xa assay was conducted at peak activity after steady state was reached. The test used to measure anti-Xa is based on the most widely used chromogenic substrate method and is the technique recommended by the College of American Pathologists [2,21]. All analyses were carried out in the same laboratory [2]. Furthermore, since the study population was very heterogeneous—in terms of treatment indications, for example—the results are likely to be applicable to the general patient population receiving therapeutic-dose enoxaparin, a factor that enhances the external validity of our results.

Conclusion

Overall, with the administration of enoxaparin at a dose of 1 mg/kg twice daily or 1.5 mg/kg once daily, only 50% of patients achieve levels of anti-Xa considered as "therapeutic", even among patients with adequate weight and renal function. Once-daily regimen tends to produce subtherapeutic levels while the twice-daily regimen tends to produce supratherapeutic levels. Among special populations, based on anti-Xa activity levels, our results suggest that dosage adjustment of enoxaparin would not be required in obese patients. However, with a twice-daily administration, increase in anti-Xa activity was observed in renally impaired patients. Given the high variability of anti-Xa activity (Fig. 1), it would be important for future studies to document anti-Xa levels to develop clinically relevant therapeutic ranges [21]. Until then, only patients in particular situations, like those renally impaired on enoxaparin administered twice daily for more than a few days,

may benefit from anti-Xa activity monitoring. Other treatment alternative, such as unfractionated heparin and eventually new antithrombotic agents with specific anti-Xa activity or direct thrombin inhibitors, may be considered as well.

Acknowledgements

The authors wish to thank all the pharmacists and physicians at the Cité de la Santé de Laval for their wonderful cooperation as well as Chantal Legris for help in preparing this manuscript and Joëlle Brassard for the revision of the manuscript. This study was made possible by a grant to the Cité de la Santé de Laval from Aventis Pharma Canada for funding of master's projects in pharmaceutical practices. Dr. Lalonde is a junior scientist (chercheur-boursier) supported by the Fonds de la recherche en santé du Québec. At the time of the study, K. Almanric, A. Bazinet, C. Brunet, and I. Turcotte were MSc students in the Faculty of Pharmacy at the University of Montreal and received financial support from the Ministry of Health, Government of Quebec.

References

[1] Weitz JI. Low-molecular-weight heparin. *N Engl J Med* 1997;**337(10)**:688—98.

[2] Hirsh J, Warkentin TE, Shaughnessy SG, Anand SS, Halperin JL, Raschke R, et al. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. *Chest* 2001;**119(1 Suppl.)** 64S—94S.

[3] Houbouyan L, Boutiere B, Contant G, Dautzenberg MD, Fievet P, Potron G, et al. Validation protocol of analytical hemostasis systems: measurement of anti-Xa activity of low-molecular-weight heparins. *Clin Chem* 1996;**42(8 Pt.1)**: 1223—30.

[4] Aventis Pharma Inc. Monographie de Lovenox (énoxaparine sodique). 14 Février 2003.

[5] Aventis Pharma Inc. Monographie de Lovenox (énoxaparine sodique). 20 Avril 2001.

[6] Nagge J, Crowther M, Hirsh J. Is impaired renal function a contraindication to the use of low-molecular-weight heparin? *Arch Intern Med* 2002;**162(22)**:2605—9.

[7] Hulot JS, Vantelon C, Urien S, Bouzamondo A, Mahe I, Ankri A, et al. Effect of renal function on the pharmacokinetics of enoxaparin and consequences on dose adjustment. *Ther Drug Monit* 2004;**26(3)**:305—10.

[8] Mismetti P, Laporte-Simitsidis S, Navarro C, Sie P, d'Azemar P, Necciari J, et al. Aging and venous thromboembolism influence the pharmacodynamics of the anti-factor Xa and anti-thrombin activities of a low molecular weight heparin (nadroparin). *Thromb Haemost* 1998;**79(6)**:1162—5.

[9] Collet JP, Montalescot G, Choussat R, Lison L, Ankri A. Enoxaparin in unstable angina patients with renal failure. *Int J Cardiol* 2001;**80(1)**:81—2.

[10] Sanderink GJ, Guimart CG, Ozoux ML, Jariwala NU, Shukla BX, Boutouyrie BX. Pharmacokinetics and pharmacodynamics of the prophylactic dose of enoxaparin once daily over 4 days in patients with renal impairment. *Thromb Res* 2002;**105(3)**:225—31.

[11] Duplaga BA, Rivers CW, Nutescu E. Dosing and monitoring of low-molecular-weight heparins in special populations. *Pharmacotherapy* 2001;**21(2)**:218—34.

[12] Becker RC, Spencer FA, Gibson M, Rush JE, Sanderink G, Murphy SA, et al. Influence of patient characteristics and renal function on factor Xa inhibition pharmacokinetics and pharmacodynamics after enoxaparin administration in non-ST-segment elevation acute coronary syndromes. *Am Heart J* 2002;**143**:753—9.

[13] Brophy DF, Wazny LD, Gehr TW, Comstock TJ, Venitz J. The pharmacokinetics of subcutaneous enoxaparin in end-stage renal disease. *Pharmacotherapy* 2001;**21(2)**:169—74.

[14] Cadroy Y, Pourrat J, Baladre MF, Saivin S, Houin G, Montastruc JL, et al. Delayed elimination of enoxaparin in patients with chronic renal insufficiency. *Thromb Res* 1991;**63(3)**:385—90.

[15] Yee JY, Duffull SB. The effect of body weight on dalteparin pharmacokinetics A preliminary study. *Eur J Clin Pharmacol* 2000;56**(4)**:293—7.

[16] Wilson SJ, Wilbur K, Burton E, Anderson DR. Effect of patient weight on the anticoagulant response to adjusted therapeutic dosage of low-molecular-weight heparin for the treatment of venous thromboembolism. *Haemostasis* 2001;**31(1)**:42—8.

[17] Harenberg J. Is laboratory monitoring of low-molecular-weight heparin therapy necessary? Yes. *J Thromb Haemost* 2004;**2(4)**:547—50.

[18] Alhenc-Gelas M, Jestin-LeGuernic C, Vitoux JF, Kher A, Aiach M, Fiessinger JN. Adjusted versus fixed doses of the low-molecular-weight heparin fragmin in the treatment of deep vein thrombosis Fragmin-Study Group. *Thromb Haemost* 1994;**71(6)**:698—702.

[19] Levine MN, Planes A, Hirsh J, Goodyear M, Vochelle N, Gent M. The relationship between the antifactor Xa level and clinical outcome in patients receiving enoxaparin low molecular weight heparin to prevent deep vein thrombosis after hip replacement. *Thromb Haemost* 1989;**62**:940—4.

[20] Rosenbloom D, Ginsberg JS. Arguments against monitoring levels of anti-factor Xa in conjunction with Low-Molecular-Weight-Heparin therapy. *Can J Hosp Pharm* 2002;**55:** 15—9.

[21] Laposata M, Green D, Van Cott EM, Barrowcliffe TW, Goodnight SH, Sosolik RC. College of American Pathologists Conference XXXI on laboratory monitoring of anticoagulant therapy: the clinical use and laboratory monitoring of low-molecular-weight heparin, danaparoid, hirudin and related compounds, and argatroban. *Arch Pathol Lab Med* 1998; **122:**799—807.

[22] Agnelli G, Iorio A, Renga C, Boschetti E, Nenci GG, Ofosu FA, et al. Prolonged antithrombin activity of low-molecular-weight heparins. *Circulation* 1995;**92:**2819—24.

[23] Handeland GF, Abildgaard U, Holm HA, Arnesen KE. Dose adjusted heparin treatment of deep venous thrombosis: a comparison of unfractionated and low molecular weight heparin. *Eur J Clin Pharmacol* 1990;**39(2)**107--12.

[24] Simonneau G, Charbonnier B, Decousus H, Planchon B, Ninet J, Sie P, et al. Subcutaneous low-molecular-weight heparin compared with continuous intravenous unfractionated heparin in the treatment of proximal deep vein thrombosis. *Arch Intern Med* 1993;**153(13)**:1541—6.

[25] Holmström M, Berglund MC, Granquist S, Bratt G, Törnebohm D, Lockner D. Fragmin once or twice daily subcutaneously in

the treatment of deep venous thrombosis of the leg. *Thromb Res* 1992;**67(1)**:49—55.
[26] Lindmarker P, Holmstrom M, Granqvist S, Johnsson H, Lockner D. Comparison of once-daily subcutaneous Fragmin with continuous intravenous unfractionated heparin in the treatment of deep vein thrombosis. *Thromb Haemost* 1994;**72(2)**:186—90.
[27] Chiquette E, Amato MG, Bussey HI. Comparison of anticoagulation clinic with usual medical care Anticoagulation control, patient outcomes, and health care costs. *Arch Intern Med* 1998;**158**:1641—7.
[28] Winter's ME. Basic clinical pharmacokinetics. 3e ed. Vancouver: Applied Thepapeutic; 1994.
[29] Shargel L, Yu ABC. Applied biopharmaceutics and pharmacokinetics. 4e éd. Stamford: Appleton & Lange; 1999.
[30] Aronoff GR. Practical guidelines for drugs dosing in patients with renal impairment. In: Schrier RW, editor. Manual of nephrology, 5th ed. Philadelphia: Lippincott Williams & Wilkins, 2000. p. 182—202.
[31] Cockroft DW, Gault H. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;**16:**31—41.
[32] Wells PS, Forgie MA, Simms M, Greene A, Touchie D, Lewis G, et al. The outpatient bleeding risk index: validation of a tool for predicting bleeding rates in patients treated for deep venous thrombosis and pulmonary embolism. *Arch Intern Med* 2003;**163(8)**:917—20.
[33] Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. *Am J Med* 1998;**105(2)**: 91—9.
[34] Hainer JW, Barrett JS, Assaid CA, Fossler MJ, Cox DS, Leathers T, et al. Dosing in heavy-weight/obese patients with the LMWH, tinzaparin: a pharmacodynamic study. *Thromb Haemost* 2002;**87(5)**:817—23.
[35] Goudable C, Saivin S, Houin G, Sie P, Boneu B, Tonthat H, et al. Pharmacokinetics of a low molecular weight heparin (Fraxiparine) in various stages of chronic renal failure. *Nephron* 1991;**59:** 543—5.
[36] Siguret V, Pautas E, Fevrier M, Wipff C, Durand-Gasselin B, Laurent M, et al. Elderly patients treated with tinzaparin (Innohep) administered once daily (175 anti-Xa IU/kg): anti-Xa and anti-IIa activities over 10 days. *Thromb Haemost* 2000;**84(5)**:800—4.
[37] Bounameaux H, de Moerloose P. Is laboratory monitoring of low-molecular-weight heparin therapy necessary? No. *J Thromb Haemost* 2004;**2(4)**:551—4.
[38] Gould MK, Dembitzer AD, Doyle RL, Hastie TJ, Garber AM. Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis A meta-analysis of randomized, controlled trials. *Ann Intern Med* 1999;**130(10)**:800—9.
[39] Cohen M, Demers C, Gurfinkel EP, Turpie AG, Fromell GJ, Goodman S, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group. *N Engl J Med* 1997;**337(7)**:447—52.
[40] Merli G, Spiro TE, Olsson CG, Abildgaard U, Davidson BL, Eldor A, et al. Subcutaneous enoxaparin once or twice daily compared with intravenous unfractionated heparin for treatment of venous thromboembolic disease. *Ann Intern Med* 2001;**134(3)**:191—202.
[41] Hirsh J, Raschke R. Heparin and low-molecular-weight heparin: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;**126(3 Suppl.)**: 188S—203S.