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Dosing in Heavy-weight/Obese Patients with the LMWH, Tinzaparin: A Pharmacodynamic Study

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Keywords

Low molecular weight heparin, tinzaparin, obesity, weight-based dosing, Innohep

Summary

This pharmacodynamic study examined weight-based dosing of the low molecular weight heparin (LMWH), tinzaparin, in heavy-weight/obese subjects. Single doses (175 and 75 IU/kg) were administered subcutaneously (SC) to 37 healthy heavy-weight subjects (101-165 kg; 26-61 kg/m²). AUA and Amax values of anti-Xa and anti-IIa activities were consistent over these body weight and body mass index (BMI) ranges, indicating that tinzaparin pharmacodynamics are not influenced by body weight or BMI. The range of AUA and Amax values in the study population overlapped that of historical control normal-weight subjects (<100 kg), indicating that weight-adjusted tinzaparin dosing yields a predictable response regardless of body weight or BMI. Tinzaparin was well tolerated, although injection site bruising was commonly reported. SC tinzaparin dosing in heavy or obese patients is appropriate based on body weight alone; the dose need not be capped at a maximal absolute dose.

Introduction

Low molecular weight heparins (LMWHs) are attractive anti-thrombotic agents for treating and preventing venous thromboembolism (VTE) as they are more bioavailable and have a less variable anticoagulant response than standard unfractionated heparin. LMWHs can be administered as a once or twice daily SC dosing regimen, and they do not require anticoagulation monitoring (1). Given that obesity is a recognized risk factor for VTE and that LMWH treatment regimens usually recommend weight-based dosing, the question persists as to whether weight-based dosing recommendations are appropriate for very heavy or obese patients. In some countries, approved dosing recommendations place a dosing "cap" at a maximum absolute allowable LMWH dose, despite patient body weight. This perspective reflects the paucity of clinical LMWH data in the obese/heavy patient.

This prospective study sought to describe the pharmacodynamic profile, in terms of anti-Xa and anti-IIa activities, of weight-based dosing regimens of the LMWH tinzaparin in heavy weight/obese subjects. For the purposes of this study, "heavy-weight/obese" refers to

subjects weighing >100 kg or whose BMI exceeds 30 kg/m²; the term was shortened to "heavy-weight". Normal-weight subjects from prior studies served as a reference population.

Subjects and Methods

Study Design

This prospective, open-label, crossover study evaluated two tinzaparin dose levels, 175 IU/kg (the FDA-approved VTE treatment dose) and 75 IU/kg (a safe and effective VTE thromboprophylaxis dose), administered SC to healthy, heavy-weight subjects (2, 3). The sequence of dose administration was by random assignment (175 followed by 75 IU/kg or 75 followed by 175 IU/kg). The treatment periods were separated by at least 1 week, and the end of study visit occurred 8 days after the second injection. The study was conducted at Quintiles Phase I Unit, Lenexa, KS, and was approved by its independent Institutional Review Board.

Subjects

Subjects were eligible for this study if they were 18 to 70 years of age and weighed between 100 and 160 kg. To assure adequate representation over this weight range, enrollment was targeted so that approximately half the subjects would weigh between 100 and 130 kg and half between 131 and 160 kg. Exclusion criteria included: 1) high risk for bleeding or thromboembolic complications; 2) clinically significant disorders, such as uncontrolled hypertension, stroke within 6 months prior to study entry, or poorly controlled diabetes mellitus; 3) use of medications that affect coagulation or platelet function, including nonsteroidal anti-inflammatory drugs within 3 days of study treatment; aspirin, clopidogrel, or ticlopidine within 10 days of study treatment; and heparin, LMWH, dextran, or warfarin within 4 weeks of study treatment; 4) smoking >2 packs of cigarettes per day; and 5) contraindication to heparin or LMWH. All subjects provided written informed consent prior to study entry.

Tinzaparin Administration

Each subject received two single doses of tinzaparin sodium (Innohep®, Bristol-Myers Squibb Company; innohep®, Leo Pharmaceuticals), separated by at least 1 week, administered SC in the anterior-lateral or posterior-lateral abdominal wall. A different site was used for each injection. The 175 IU/kg dose was prepared from vials containing a tinzaparin concentration of 20,000 IU/mL, and the 75 IU/kg dose from vials containing a concentration of 10,000 IU/mL. All doses were measured with a 1-mL tuberculin type syringe [a table of calculated doses based on body weight, in 5-lb (2.2-kg) increments, was provided in the study protocol]. When calculating the weight-adjusted dose, the investigator rounded to the nearest weight category provided in the table. If the calculated volume exceeded 1.0 mL, a 3-mL syringe was used for administration. Specifically, 1 mL of tinzaparin was measured in the 1-mL syringe and then transferred to the 3-mL syringe; the 1-mL syringe was re-used to measure the additional required amount of tinzaparin, which was also added to the 3-mL

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Table 1 Demographics

Gender: Male	N (%)	22 (59.5)
Female		15 (40.5)
Race: White	N (%)	23 (62.2)
Black		11 (29.7)
Hispanic		2 (5.4)
American Indian/Alaskan Native		1 (2.7)
Age [years]	Mean (SD)	35.4 (11.4)
	Min, Max	19, 69
Weight [kg]	Mean (SD)	129.6 (20.5)
	Min, Max	101.1, 165.1
Height [cm]	Mean (SD)	174.6 (10.3)
	Min, Max	155.0, 198.0
Body Mass Index [kg/m ²]	Mean (SD)	43.0 (8.7)
	Min, Max	26.3, 61.3
Body Mass Index [kg/m ²]: <30	N (%)	1 (2.7)
30 to <40		15 (40.5)
40 to <45		4 (10.8)
≥45		17 (45.9)

syringe. The calculated dose was given as a single injection; dose splitting was not permitted.

Sampling Procedures and Analytical Methodology

Following each tinzaparin administration, blood samples were drawn over the next 30 hours to assess pharmacodynamic biomarkers (anti-Xa and anti-IIa

activities). Sample times relative to administration were -0.25, 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, and 30 h.

Sodium citrated plasma samples were analyzed for anti-Xa activity (primary measure) and anti-IIa activity (secondary measure) per the method described by Mätzsch (4). The specific methods used for determining the anti-Xa and anti-IIa activities of tinzaparin in human platelet-poor plasma were based on procedures and reagents supplied with commercially available

Parameter		Anti-Xa Activity		Anti-IIa Activity	
		75 IU/kg	175 IU/kg	75 IU/kg	175 IU/kg
Tmax [h]	N	37	35	37	35
	Median	4.0	4.0	4.0	5.0
	Min, Max	1.5, 8.1	3.0, 8.0	2.0, 8.1	1.5, 8.0
t _{1/2} [h]	N	36	35	33	35
	Mean (SD) ^a	3.85 (1.09)	4.23 (0.98)	5.33 (2.06)	5.39 (1.96)
	CV (%)	28	23	39	36
λ [h ⁻¹]	N	36	35	33	35
	Mean (SD)	0.18 (0.05)	0.16 (0.04)	0.13 (0.05)	0.13 (0.05)
	CV (%)	28	23	39	36
Amax [IU/mL]	N	37	35	37	35
	Mean (SD)	0.34 (0.11)	0.81 (0.15)	0.12 (0.05)	0.34 (0.10)
	CV (%)	33	19	40	29
CL [L/h]	N	36	35	33	35
	Mean (SD)	3.11 (0.85)	2.40 (0.97)	9.01 (4.01)	5.71 (2.24)
	CV (%)	27	40	45	39
AUA [IU•h/mL]	N	36	35	33	35
	Mean (SD)	3.29 (0.84)	9.99 (1.99)	1.21 (0.37)	4.34 (1.26)
	CV (%)	25	20	30	29
AUAT [IU•h/mL]	N	37	35	37	35
	Mean (SD)	2.87 (1.00)	9.54 (1.97)	0.78 (0.48)	3.53 (1.03)
	CV (%)	35	21	62	29

^aHarmonic mean and pseudo-standard deviation based on the jackknife variance technique.

Tmax=time to maximal observed activity; t_{1/2}=terminal disposition half-life; λ=terminal rate constant;

Amax=observed maximal activity; CL=clearance; AUA=area under the activity-time curve to infinity;

AUAT=area under the activity-time curve to the last quantifiable measure; CV=coefficient of variation

Note: Subjects who had insufficient data in the terminal phase were not included in pharmacodynamic parameter calculations.

Table 2 Pharmacodynamic parameters for heavy-weight subjects following a 75 IU/kg and 175 IU/kg SC injection of tinzaparin

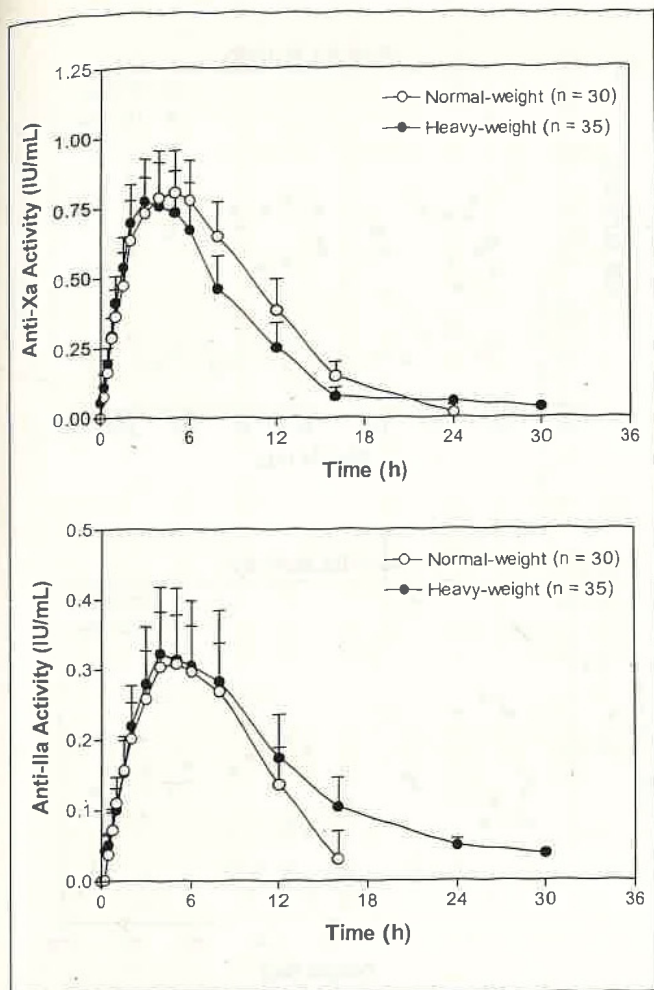
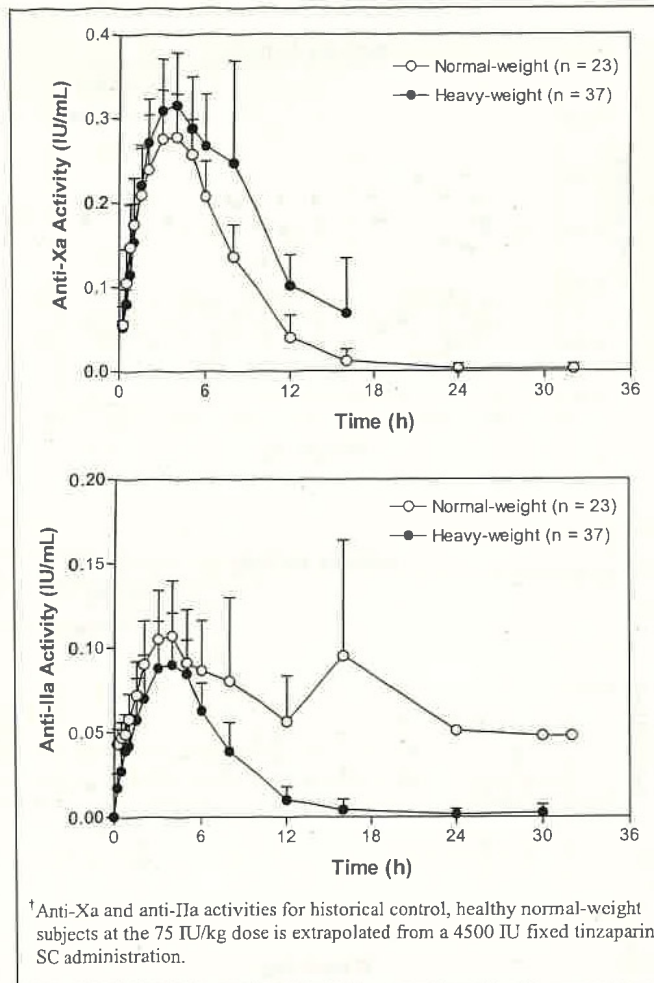


Fig. 1 Mean (SE) anti-Xa and anti-IIa activity in heavy-weight and historical control healthy normal-weight subjects receiving 175 IU/kg tinzaparin via SC injection



[†]Anti-Xa and anti-IIa activities for historical control, healthy normal-weight subjects at the 75 IU/kg dose is extrapolated from a 4500 IU fixed tinzaparin SC administration.

Fig. 2 Mean (SD) anti-Xa and anti-IIa activity in heavy-weight and historical control healthy normal-weight subjects receiving 75 IU/kg[†] tinzaparin via SC injection

chromogenic assay kits (Diagnostica Stago and American Diagnostica Actichrome, respectively) validated at MDS Pharma Services (St. Laurent, Montreal, Canada). The anti-Xa/anti-IIa analytical methods were optimized as previously described (5) to reduce the contributions of endogenous agents and sample handling to assay result variability. The validated assay ranges were 0.030 to 0.400 IU/mL for anti-Xa and 0.020 to 0.252 IU/mL for anti-IIa.

Pharmacodynamic Analyses

Anti-Xa and anti-IIa activities expressed in IU/mL were used to derive Amax (maximal observed activity), AUA (area under the activity-time curve to infinity), Tmax (time of observed maximal activity), $t_{1/2}$ (disposition half-life), CL (clearance), and λ (elimination phase rate constant) using noncompartmental analyses. The harmonic mean and pseudo-standard deviation were calculated for $t_{1/2}$ based on the jackknife variance technique. Prior to analysis, Amax and AUA values were transformed using the natural logarithm.

Safety Assessments

Safety assessments consisted of monitoring adverse experiences, including bleeding-related events; clinical laboratory tests; physical examinations; and vital signs. Injection-site hematoma was defined as a palpable or visible mass of ≥ 2 cm in diameter at the injection site.

Sample Size

The trial was designed to detect a 20% difference in anti-Xa parameters (Amax and AUA) using 95% confidence intervals for the heavy/obese subjects relative to normal-weight subjects administered similar doses in prior studies. It was hypothesized that if the 95% confidence interval for the heavy-weight subjects did not overlap the 95% confidence interval for the normal-weight historical control subjects, then the two group means would be considered different.

Comparison with Historical Normal-Weight Controls

Measures of central tendency with corresponding variance for anti-Xa and anti-IIa measures were calculated by dose level (175 IU/kg and 75 IU/kg). The 95% confidence interval for each measure was the basis for comparisons to historical control normal-weight (<100 kg) healthy subject data. As subjects from one of the control studies were not dosed on a weight-adjusted basis, but rather received a fixed 4500 IU dose (~ 64 IU/kg), their data were adjusted for weight and scaled to 75 IU/kg (assuming linear pharmacodynamics).

Statistical Analyses

A result was deemed statistically significant when the test statistic yielded a two-tailed probability of 0.05 or less, or when confidence intervals failed to overlap. Confidence intervals were derived using normal theory based on the student's *t*-distribution. Baseline values for all data were defined as the last

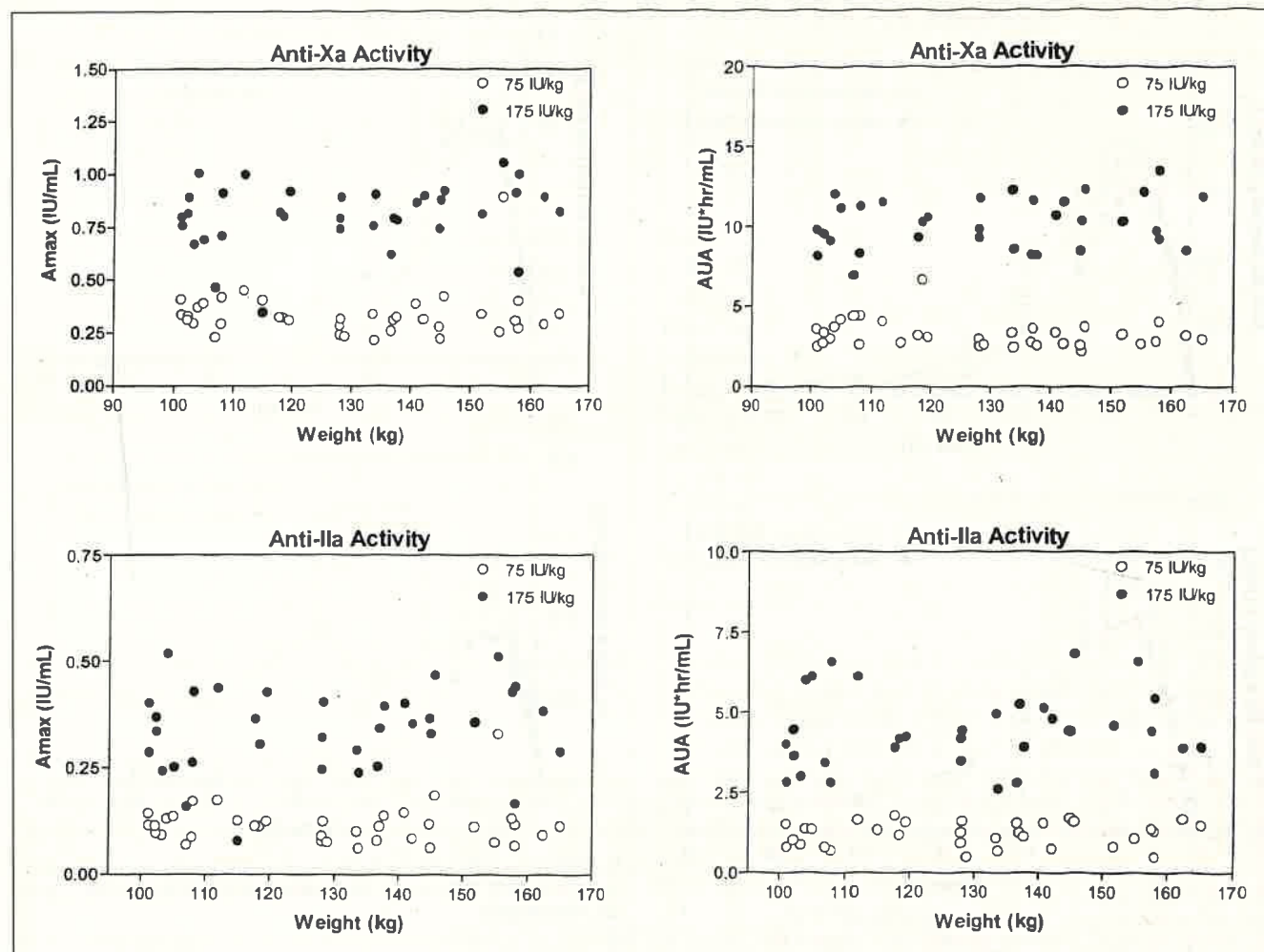


Fig. 3 Amax and AUA versus body weight based on anti-Xa and anti-IIa activity following 75 IU/kg and 175 IU/kg SC injections of tinzaparin in heavy-weight subjects

measurements taken prior to (screening and baseline) the first dose of study drug. By-period analyses used period-specific baseline values. As pre-dose activity levels were below the quantification limit, no baseline adjustment of activity was necessary. Data were pooled by dose across sequences as there were no statistically

significant carryover or sequence effects with respect to the primary anti-Xa measures of Amax and AUA. Linear regression models evaluated Amax and AUA as dependent variables for relationships with weight and BMI (test of slope = 0). All statistical analyses were performed using SAS® (Version 6.12).

Parameter	75 IU/kg ^a			175 IU/kg		
	N	Mean	(95% CI)	N	Mean	(95% CI)
Anti-Xa Activity						
<u>AUA (IU•h/mL)</u>						
Normal-Weight	27	2.36	(2.164, 2.556)	28	9.55	(8.961, 10.139)
Heavy-Weight	36	3.29	(3.017, 3.565)	35	9.99	(9.336, 10.652)
<u>Amax (IU/mL)</u>						
Normal-Weight	27	0.30	(0.281, 0.319)	30	0.87	(0.784, 0.956)
Heavy-Weight	37	0.34	(0.303, 0.375)	35	0.81	(0.759, 0.859)
Anti-IIa Activity						
<u>AUA (IU•h/mL)</u>						
Normal-Weight	23	0.77	(0.680, 0.860)	27	3.53	(3.278, 3.782)
Heavy-Weight	33	1.21	(1.088, 1.340)	35	4.34	(3.926, 4.760)
<u>Amax (IU/mL)</u>						
Normal-Weight	23	0.10	(0.088, 0.112)	30	0.33	(0.304, 0.356)
Heavy-Weight	37	0.12	(0.103, 0.133)	35	0.34	(0.307, 0.373)

^aAnti-Xa and anti-IIa activities for historical control, healthy normal-weight subjects at the 75 IU/kg dose is extrapolated from a 4500 IU fixed tinzaparin SC administration.

Table 3 Mean anti-Xa and anti-IIa activities of Amax and AUA with 95% confidence intervals for heavy-weight subjects and for historical control normal-weight subjects

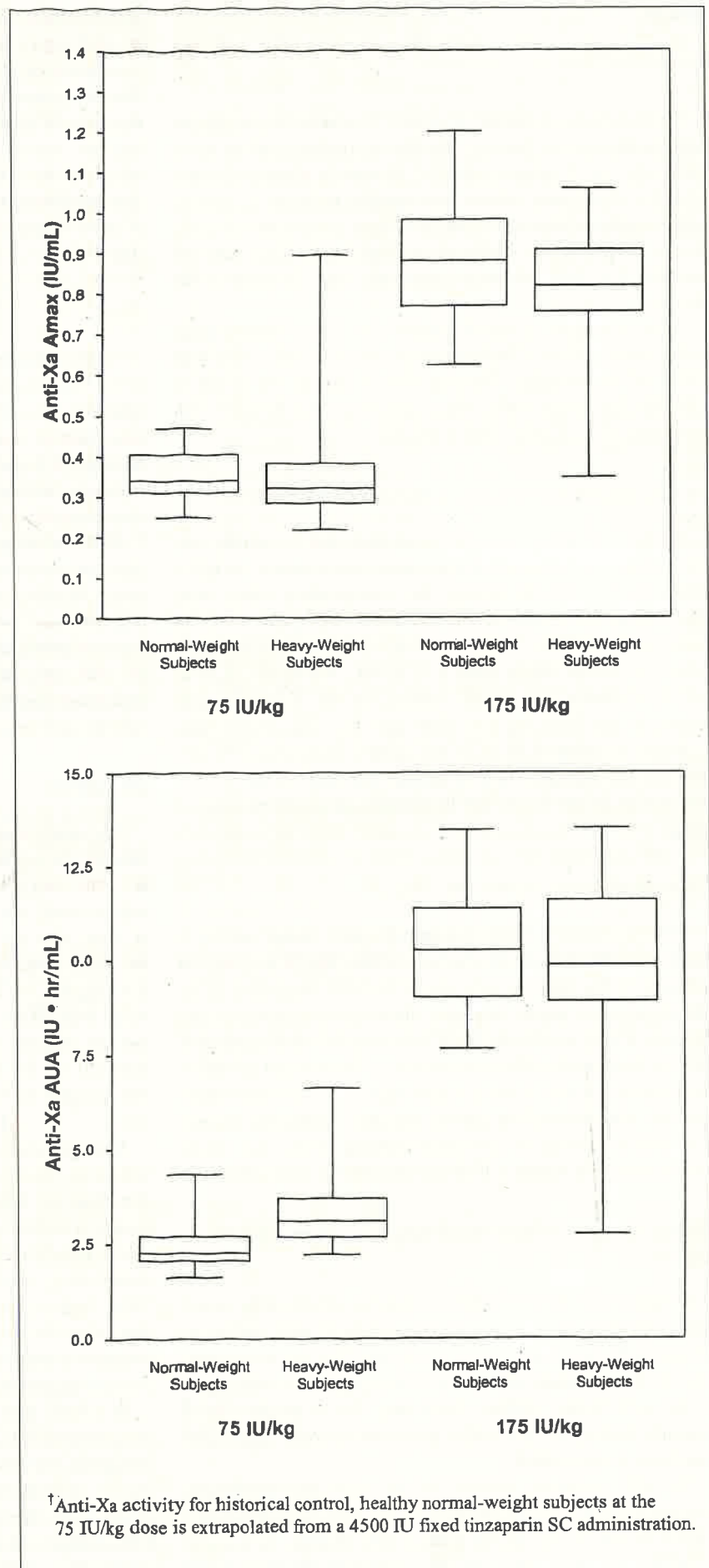


Fig. 4 Box plots of AUA and Amax based on anti-Xa activity following 75 IU/kg[†] and 175 IU/kg SC injections of tinzaparin in normal-weight subjects and heavy-weight subjects

[†]Anti-Xa activity for historical control, healthy normal-weight subjects at the 75 IU/kg dose is extrapolated from a 4500 IU fixed tinzaparin SC administration.

Results

Subject Disposition

The study protocol required 32 subjects. To account for two subjects who discontinued (one because of an adverse experience and one lost to follow-up) and 3 subjects who had incomplete pharmacodynamic data, five replacement subjects were enrolled to ensure 32 subjects with complete profiles. As a result, 37 subjects received the 175 IU/kg dose of tinzaparin and 35 subjects received the 75 IU/kg dose. All available data from all study participants were included in the analyses.

Of the 37 subjects, 22 were men and 15 were women. Demographics are presented in Table 1. The body weights of the subjects ranged from 101 to 165 kg; 19 subjects weighed between 100 and 130 kg and 18 subjects weighed over 130 kg. BMIs ranged from 26 to 61 kg/m², with 21 subjects (57%) having a BMI $\geq$ 40 kg/m².

Pharmacodynamics of Tinzaparin in Heavy-Weight Subjects

For the 175 IU/kg dose, the mean peak anti-Xa activity was 0.81 IU/mL at a median of 4.0 h post-dose, with a mean $t_{1/2}$ of 4.23 h (Table 2). For anti-IIa activity, the corresponding values were 0.34 IU/mL, 5.0 h, and 5.39 h. For the 75 IU/kg dose, anti-Xa Amax was 0.34 IU/mL, T_{max} was 4.0 h, and $t_{1/2}$ was 3.85 h, and the respective anti-IIa values were 0.12 IU/mL, 4.0 h, and 5.33 h. Anti-Xa clearance was slightly reduced for the 175 IU/kg dose relative to the 75 IU/kg dose (2.40 and 3.11 L/h, respectively). Exposure, as measured by AUA, was slightly greater-than-dose proportional for both anti-Xa and anti-IIa measures. Mean activity-time profiles for anti-Xa and anti-IIa measures are illustrated in Figs. 1 and 2.

Effect of Body Weight and Body Mass Index

The relationship between pharmacodynamics (Amax and AUA based on anti-Xa and anti-IIa activities) and body weight are presented in Figure 3. The findings were similar for BMI. Regardless of the pharmacodynamic metric, these plots illustrate consistent values over the range of body weights and BMIs, indicating that when tinzaparin is dosed by body weight, there is no influence of body weight or BMI on the pharmacodynamics in heavy-weight subjects. Minimal intersubject variation was observed for anti-Xa measures. Regression analyses confirmed the absence of correlations between anti-Xa and anti-IIa activities and body weight or BMI (test of slope = 0; not significant).

Pharmacodynamics in Heavy-Weight Subjects vs. Normal-Weight Subjects

Comparisons of the activity-time courses for subjects in the current study with those from normal-weight subjects in prior studies are provided in Figures 1 and 2 for 175 IU/kg and 75 IU/kg, respectively. Overall, there is considerable overlap in these populations with respect to the activity-time profiles, illustrating that a weight-adjusted tinzaparin dosing paradigm yields a predictable response regardless of dose, body weight, or BMI.

The 95% confidence intervals for the mean pharmacodynamic measures for normal-weight and heavy-weight subjects are presented in Table 3 for anti-Xa activity, the primary study measure. At a dose of 175 IU/kg, the mean Amax and AUA values for the heavy-weight

subjects were not different from those for normal-weight subjects dosed at 175 IU/kg, i.e., the confidence intervals overlap.

At a dose of 75 IU/kg, the mean Amax value for the heavy-weight subjects was not different from the mean for the normal-weight subjects dosed at 4500 IU with the values scaled to 75 IU/kg, i.e., the confidence intervals overlap. The mean AUA was higher in the heavy-weight subjects (the confidence intervals did not overlap), but the absolute difference in AUA was small as illustrated in summary plots of heavy-weight and normal-weight subject data for AUA and Amax (Fig. 4).

Safety

Adverse experiences were reported for 24 of 37 study subjects (65%) following the 75 IU/kg dose and for 32 of 35 subjects (91%) following the 175 IU/kg dose. The majority of adverse experiences were mild to moderate, and primarily consisted of injection site bruising (32 subjects overall). The frequencies of adverse experiences reported within the two body weight strata (100 to 130 kg and >130 kg) were comparable.

Thirty-two subjects experienced bleeding-related adverse experiences (injection site bruising and/or ecchymosis), but there were no major or serious bleeding events. Although there was a dose-bleeding event effect (11 subjects had an event only after the 175 IU/kg dose while 3 had a bleeding-related event only after the 75 IU/kg dose), there was no relationship between the incidence of bleeding-related adverse experiences and the volume of the administered dose (which was weight-based) for either tinzaparin dose level.

Discussion

This study sought to determine whether the pharmacodynamic rationale for weight-based tinzaparin dosing, which was established in normal-weight healthy subjects and validated in clinical efficacy studies, would also hold for patients with above-normal body weight or those who are obese. To assure adequate representation over the weight range of interest in this study (100 to 160 kg), enrollment was targeted so that approximately half of the subjects would weigh from 100 to 130 kg and half from 131 to 160 kg. Enrollment met this objective of a wide distribution of body weights, ranging from 101 to 165 kg. Forty-six percent of the subjects had BMIs that exceeded the 99th percentile for the U.S. population ($\geq$ 45 kg/m²) (6).

When tinzaparin is administered at fixed doses, independent of body weight, to normal-weight subjects (52-93 kg), anti-Xa activity is dependent on both dose and body weight (7). However, when tinzaparin is dosed on a body weight basis to normal-weight subjects (56-93 kg) (5) or to heavy-weight subjects (101-165 kg) as in the current study, anti-Xa activity is not correlated with body weight. These findings suggest that weight-based dosing of tinzaparin is appropriate for subjects regardless of body weight. Previously reported tinzaparin population pharmacokinetic analyses of clinical study subjects also support the dosing of tinzaparin on a body-weight basis (8).

In general there is limited information available regarding the administration of LMWHs to heavy-weight patients. For dalteparin and enoxaparin, reports suggest that weight-based dosing is appropriate and requires no additional adjustment (9, 10). A recent review of LMWH dosing in special populations (11) suggested that body surface area and BMI correlate with anti-Xa activity and also with bleeding risk or VTE complications. Although anti-Xa activity is generally used as the bio-

marker for heparins as heparin itself cannot be measured directly, the correlation between anti-Xa activity and the clinical efficacy and safety of these agents is not well established. More to the point, integrated safety analyses from tinzaparin clinical studies do not indicate altered efficacy or increased bleeding risk for subjects with BMI >30 kg/m² (12).

It is important to note that regulatory and expert agencies clearly recognize that LMWHs are produced by different processes and are not interchangeable (13). Accordingly, the findings of the current study should be considered specific to tinzaparin. While the data in this study represent relatively healthy, heavy subjects, weighing between 100 and 165 kg, with normal renal functioning, the anti-Xa and IIa activities are consistent across a wide range of weights and BMIs, i.e., there are no trends suggesting that the relationships would not hold above a specific weight.

The study's safety findings are comparable to those in prior healthy subject and clinical studies, i.e., tinzaparin is well tolerated and significant bleeding is uncommon. While injection site hematoma is a recognized but uncommon tinzaparin-related adverse experience, none were observed in this study. Bruising at the injection site was common and was somewhat more frequent at the 175 IU/kg treatment dose than the 75 IU/kg prevention dose, but this was not related to the volume of tinzaparin administered.

In conclusion, this study supports the recommendation that SC dosing of tinzaparin to heavy-weight or obese patients can be based on body weight alone. There was no evidence suggesting that the dose of tinzaparin should be capped at a maximal fixed dose or that further adjustments for weight or obesity are required.

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