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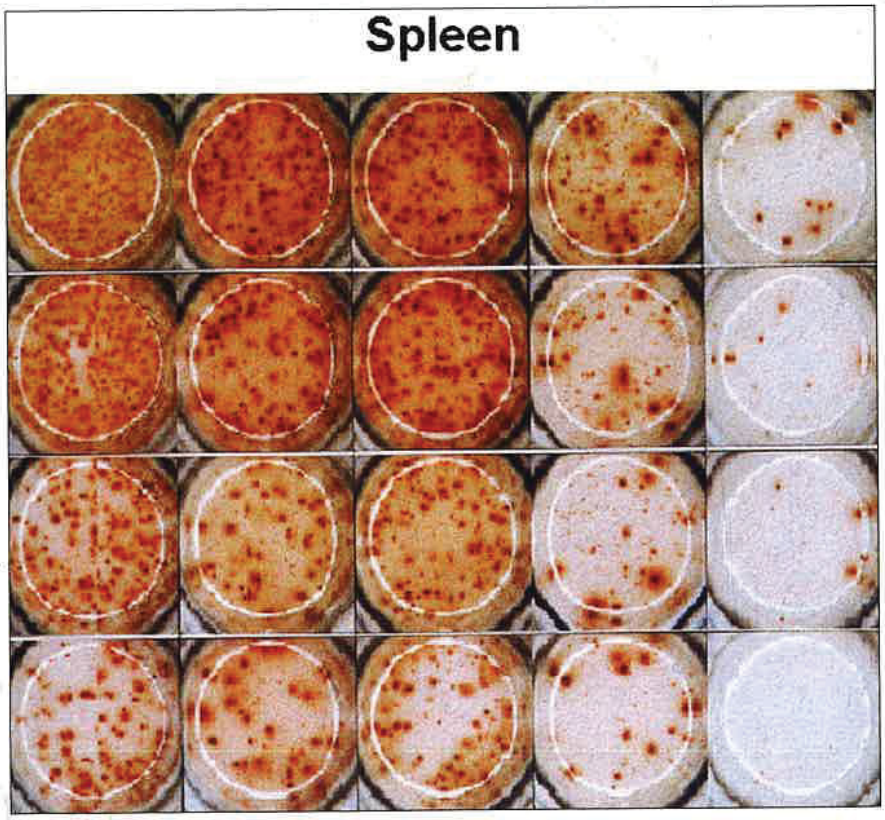

LETTERS TO THE EDITOR

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

James W. Hainer[1], Jeffrey S. Barrett[2], Christopher A. Assaid[1], Michael J. Fossler[2], Donna S. Cox[2], Todd Leathers[1], Philip T. Leese[3]

[1]Bristol-Myers Squibb Company, Wilmington DE and [2]Newark DE; [3]Quintiles Phase I Services, Lenexa KS, USA

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/m^2). 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 antithrombotic 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/m^2; 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

Correspondence to: James W. Hainer, M.D., M.P.H., 2307 Pawlawyn Road

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

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

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
t½ [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

[a]Harmonic mean and pseudo-standard deviation based on the jackknife variance technique.
Tmax=time to maximal observed activity; t½=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

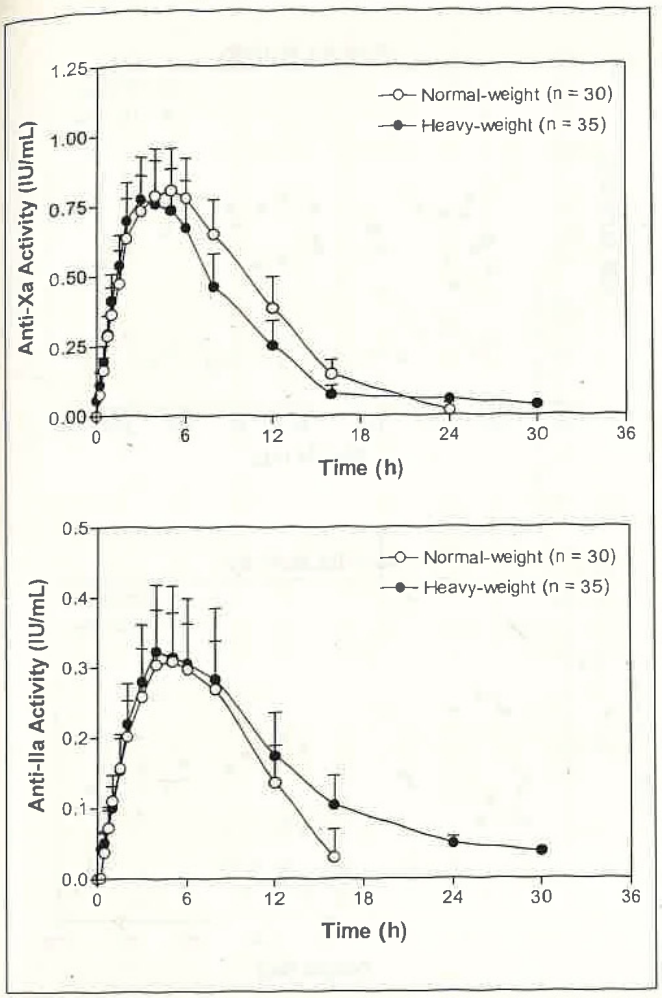
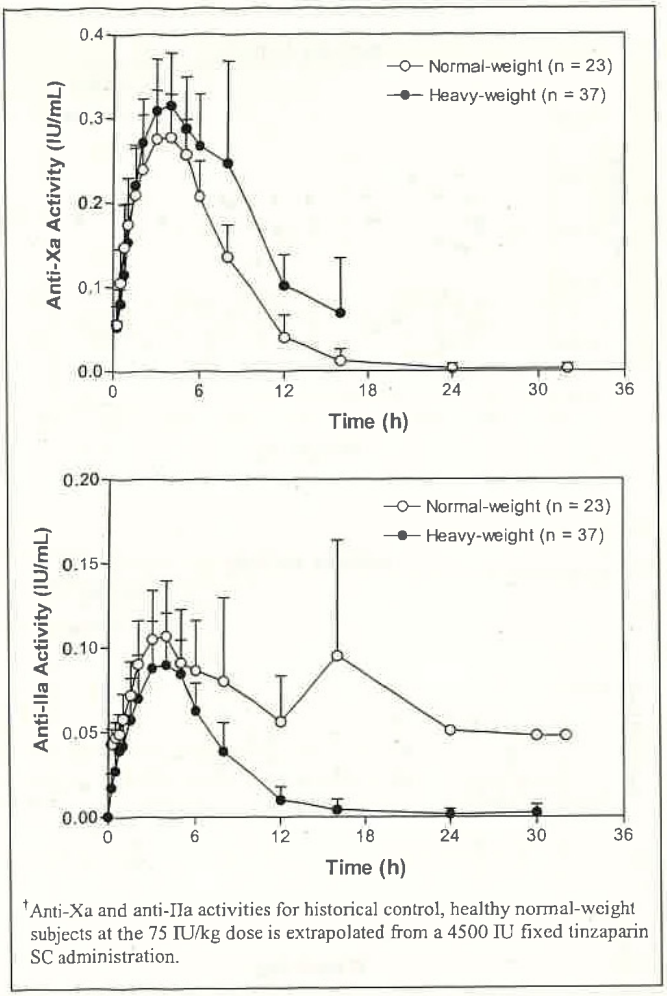


Fig. 1 Mean (SE) anti-Xa and anti-IIa activity in heavy-weight and historical control healthy normal-weight subjects receiving 175 IU/kg tinzaparin via SC injection



†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), t½ (disposition half-life), CL/F (clearance), and λ (elimination phase rate constant) using noncompartmental analyses. The harmonic mean and pseudo-standard deviation were calculated for t½ 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

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

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