Dosing of Unfractionated Heparin in Obese Patients with Venous Thromboembolism

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BACKGROUND: Aggressive weight-based dosing guidelines help achieve prompt therapeutic anticoagulation in patients with venous thromboembolism (VTE). While obese patients with VTE face an increased risk of recurrence, physicians typically resist prescribing doses two to three times the usual dose because of concern about bleeding complications.

OBJECTIVE: To examine the use of unfractionated heparin in obese patients with VTE at an academic teaching hospital in order to document the extent and pattern of underprescribing in this high-risk patient population.

DESIGN: Three-year, cross-sectional consecutive case series.

PATIENTS: Adult inpatients with VTE and a body mass index ≥ 30 kg/m² who were treated with unfractionated heparin.

MEASUREMENTS: Time to achievement of therapeutic anticoagulation (activated partial thromboplastin time >60 s) and gap between recommended and prescribed heparin doses.

RESULTS: Time to attainment of therapeutic anticoagulation exceeded 24 h in 29% of study patients ($n=84$) and exceeded 48 h in 14% of patients. In 75 patients (89%), the prescribed bolus dose fell below the recommended dose of 80 units/kg, and in 64 patients (76%) the initial continuous infusion fell more than 100 units/h below—in some cases more than 1000 units/h below—the recommended dose of 18 units/kg/h. There was a significant correlation between time to therapeutic anticoagulation and initial infusion dose (Spearman $r=-0.27$; $p<0.02$). Each decrease of 1 unit/kg/h translated to a delay ranging from about 0.75 h to 1.5 h over the range of prescribed doses (6 to 22 units/kg/h).

CONCLUSIONS: A substantial proportion of obese patients treated with unfractionated heparin experienced a delay >24 h in achieving adequate anticoagulation, and the vast majority received an inadequate heparin bolus or initial continuous infusion (or both) according to current dosing guidelines.

KEY WORDS: anticoagulants/administration & dosage; body weight; heparin/therapeutic use; obesity; thromboembolism/drug therapy.

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A mong survivors of venous thromboembolism (VTE), 30% experience a recurrence within 10 years.¹ Because the risk of recurrence increases in proportion to body mass index, individuals who are overweight or obese face nearly double the risk observed in normal-weight patients.² To minimize the likelihood of recurrent VTE, aggressive weight-based dosing formulas have been developed to help achieve prompt therapeutic anticoagulation with unfractionated heparin.³ These formulas assume that (a) exceeding the therapeutic threshold within the first 24 hours after diagnosis lowers the subsequent risk of recurrence,^{4,5} and (b) high initial doses of heparin that may produce supratherapeutic partial thromboplastin times in patients with VTE do not appreciably increase the likelihood of bleeding complications.⁴ In obese patients, these weight-based formulas yield exceptionally high initial heparin doses.

Anecdotal observations at our hospital and published reports from other institutions⁶ suggest that physicians frequently deviate from dosing guidelines when ordering initial anticoagulant therapy in obese patients with VTE. Our hospital uses a standardized order set specifying a weight-based initial heparin bolus and infusion rate for patients with VTE or acute coronary syndromes who require anticoagulation. Nevertheless, physicians typically resist prescribing doses in obese patients that would be two to three times the "standard-care" dose, perhaps believing that such large initial doses pose an unacceptably high risk of bleeding complications. The purpose of the present study was to examine the use of unfractionated heparin in obese patients with VTE at an academic teaching hospital in order to document the extent and pattern of underprescribing in this high-risk patient population.

METHODS

Patient Inclusion Criteria

Winthrop University Hospital is a 595-bed academic teaching hospital located on Long Island, New York. This cross-sectional study examined data from a consecutive series of adult inpatients with a body mass index ≥ 30 kg/m² who were

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treated at Winthrop with unfractionated heparin for pulmonary embolism or deep vein thrombosis between January 1, 2004 and December 31, 2006. To be included, a patient must have received continuous unfractionated heparin therapy that eventually led to an activated partial thromboplastin time (PTT) exceeding 60 s, which corresponds to a factor Xa level >0.3 units in the hospital's clinical laboratory.

Data Collection

Patients were identified from a review of the log books of the Department of Radiology and Nuclear Medicine listing all patients with a lung perfusion scan, computed tomographic pulmonary angiogram, or duplex ultrasound. Hospital medical records of all patients meeting the inclusion criteria were reviewed and pertinent data recorded on a standardized form. These data included patient age, sex, height, weight, method of diagnosis, date and time of initial treatment with heparin, initial bolus and infusion rate, date and time when the PTT first exceeded 60 s, and final infusion rate that sustained a PTT within the range of 60-90 s. The study was approved by the hospital's institutional review board.

Analysis

The number of hours to achievement of therapeutic anticoagulation was defined as the interval between initiation of heparin therapy and attainment of PTT >60 s.

Bolus. The analysis compared the recommended dose (80 units/kg of body weight)⁵ to the actual prescribed doses. ("Body weight" is sometimes referred to as "actual body weight" in other publications to distinguish it from "ideal body weight.") Nonparametric correlation analysis was used to investigate the relationship between time to therapeutic anticoagulation and bolus dose (units) and between time and weight-adjusted dose (units/kg).

Continuous Infusion. Nonparametric correlation analysis and simple linear regression analysis were used to examine the relationship between body weight and (a) the prescribed initial continuous infusion rate, and (b) the final rate that achieved a therapeutic effect, and to compare each of these with the recommended initial infusion rate of 18 units/kg/h.⁵ Scatter plots and histograms were constructed to display and summarize the observed prescribing patterns. Nonparametric correlation and linear regression were used to examine the relationship between time to therapeutic effect and initial continuous infusion dose (units/h) and between time and weight-adjusted dose (units/kg/h).

RESULTS

During the period of the study, 84 patients with a documented venous thromboembolism had a body mass index ≥ 30 kg/m² and received unfractionated heparin therapy (Table 1). The time to achievement of PTT >60 s ranged from 4 to 96 h, with a median (interquartile range) of 18.5 h (8 to 41 h). Of the 84

study patients, 24 (28.6%) failed to achieve this goal within 24 h, and 12 patients (14.3%) still had not achieved the goal by 48 h (Fig. 1).

Bolus

Study patients received a heparin bolus of 6949 ± 2560 units (mean $\pm$ SD) (range: 0 to 18,000 units), or 58 ± 25 units/kg (range: 0 to 137 units/kg). In 75 of 84 patients (89.3%), the prescribed dose fell below the recommended dose of 80 units/kg. The mean recommended and prescribed doses differed by 37.9% $([80-58]/80)$. There was no significant correlation between time to therapeutic effect and prescribed dose (Spearman $r = -0.13$; $p = 0.23$) or between time and dose/kg (Spearman $r = -0.19$; $p = 0.09$).

Continuous Infusion

Patients received an initial continuous infusion of 1450 ± 462 units/h (range: 700 to 2700 units/h) or 13 ± 4 units/kg/h (range: 6 to 22 units/kg/h). Most study patients (64 patients, or 76.2%) received an initial infusion dosed more than 100 units/h below—in some cases more than 1000 units/h below—the recommended dose of 18 units/kg/h (Figs. 2 and 3). It is evident from Fig. 2 that physicians frequently prescribed a "standard-care" infusion of 1000 units/h irrespective of body weight. In fact, 28.6% of patients (24/84) received that dose. Using the 18 units/kg/h formula, the mean recommended infusion rate was 1990 ± 478 units/h. Therefore, the difference between recommended and prescribed doses averaged 27.1% $([1990-1450]/1990)$. In contrast, the final therapeutic dose of 1576 ± 478 units/h (range: 750 to 4000 units/h) differed from the initial prescribed dose by an average of only 8.0% $([1576-1450]/1576)$. The regression analysis revealed a pattern of initial continuous infusions that fell well below the recommended dose but not far from the final dose that ultimately achieved therapeutic anticoagulation (Spearman $r = 0.43$; $p < 0.001$ for the correlation between body weight and initial continuous infusion; Spearman $r = 0.63$; $p < 0.001$ for the correlation between body weight and final therapeutic dose) (Fig. 4). The histogram in Fig. 5 summarizes the data comparing the recommended and prescribed initial doses with the final therapeutic dose.

There was no significant correlation between time to therapeutic effect and initial dose in units/h (Spearman $r = -0.18$; $p = 0.10$), but a significant correlation between time and dose in units/kg/h (Spearman $r = -0.27$; $p < 0.02$).

Table 1. Patient Characteristics. N=84

Sex	Female: 48 (57.1%)	
Age (yr)	Mean $\pm$ SD: 57.1 ± 17.8	Range: 22 to 91
Weight (kg)	Median: 105.5	Range: 60 to 181
Body Mass Index (kg/m ²)	Median: 36.6	Range: 30.0 to 62.3
Diagnosis	Pulmonary embolus: 80 ^a	Deep vein thrombosis: 4 ^b

^a68 diagnosed by computed tomographic pulmonary angiography and 12 by ventilation/perfusion lung scan

^bDiagnosed by duplex ultrasound

Figure 1. Hours required to achieve therapeutic anticoagulation (partial thromboplastin time >60 s). N=84.

To quantify the delay attributable to underdosing, we conducted a regression analysis after performing a log transformation to normalize the time interval data, which is clearly skewed (Fig. 1). This analysis revealed that each decrease of 1 unit/kg/h translated to a delay ranging from about 0.75 h to 1.5 h over the range of prescribed doses (6 to 22 units/kg/h) (Pearson $r^2=0.07$; $p<0.02$).

DISCUSSION

Prompt achievement of therapeutic anticoagulation reduces the risk of recurrence in patients with VTE,³ but physicians

Figure 2. Initial continuous heparin infusion compared with recommended dose of 18 units/kg/h. Each dot represents 1 patient. N=84.

Figure 3. Gap between recommended and actual initial continuous heparin doses. Histogram shows number of patients receiving initial continuous heparin doses that fell below or above the recommended dose (18 units/kg/h) by the indicated amounts (units/h). N=84.

often deviate from weight-based dosing guidelines for the initial treatment of this condition⁶ even when a hospital incorporates the guidelines into a standard order set. In the case of obese patients, the clinician may be concerned that the recommended initial therapy with unfractionated heparin could be excessive and lead to bleeding complications. In the present investigation, the vast majority of obese patients received a bolus and an initial continuous infusion that fell well below the recommended doses of 80 units/kg and 18 units/kg/h, respectively. Physicians sometimes substituted a fixed, lower-dose infusion, possibly based on their experience and comfort with heparin dosing guidelines for patients with

Figure 4. Initial continuous heparin infusion, recommended dose, and final therapeutic dose with corresponding dose-vs.-weight regression lines. The regression analysis revealed a pattern of initial continuous infusions that fell well below the recommended dose but not far from the final dose that ultimately achieved therapeutic anticoagulation (Spearman $r=0.43$; $p<0.001$ for the correlation between body weight and initial continuous infusion; Spearman $r=0.63$; $p<0.001$ for the correlation between body weight and final therapeutic dose). Each dot represents 1 patient. N=84.

Figure 5. Relationship between prescribed initial heparin dose and final therapeutic dose and between recommended initial dose and final dose. Histogram shows number of patients whose initial continuous heparin infusion doses fell below or above the final therapeutic dose by 100 units/h or more, as well as the number of patients whose initial doses would have fallen below or above the therapeutic dose by that amount had the initial dosing guideline (18 units/kg/h) been followed. N=84.

ischemic heart disease that specify an upper limit of 1000 units/h.^{5,7} In fact, nearly 30% of study patients received a fixed initial infusion of 1000 units/h, far below the recommended dose for these obese patients with VTE.

In 50% of patients, physicians prescribed initial doses that anticipated the final therapeutic dose within 100 units/h (Fig. 5). Had they adhered to the guideline, they would have come this close in only 14% of patients, while 80% of patients would have received a supratherapeutic dose and 6% a subtherapeutic dose. This prescribing pattern suggests that physicians may have been choosing initial doses intended to approximate the final therapeutic dose rather than choosing initial doses expected to overshoot the target in order to attain therapeutic anticoagulation as rapidly as possible—the strategy built into the 18 units/kg/h formula.^{3,8}

To check the plausibility of this hypothesis informally, one of us (AH) separately interviewed a convenience sample of 8 (of 81) internal medicine residents, asking if they could explain our study findings. All 8 residents indicated awareness of the weight-based guidelines but explained that concerns about bleeding cause them to modify the guidelines downward in obese patients. Some residents also stated that they believed the guidelines specified an upper limit for the heparin dose, as in the case of the anticoagulation guidelines for acute coronary syndromes, although the hospital's heparin dosing algorithm specifies no such limit for patients with VTE.

In view of evidence that supratherapeutic partial thromboplastin times do not increase bleeding complications in patients with VTE,^{9,10} along with evidence that prompt anticoagulation reduces the risk of recurrence,^{4,11} residents' misperceptions may cause delays having serious consequences. In the present study, the time to attainment of therapeutic anticoagulation exceeded 24 h in 29% of study patients and exceeded 48 h in 14% of patients (Fig. 1). It is troubling to note that the gap between the recommended and prescribed initial continuous heparin infusion increased with body weight—by about 100 units/h for each 10-kg increase in body weight (Fig. 4). Furthermore, the relative size of the gap as a

percentage of the recommended dose also increased with body weight, thereby magnifying the risk of harm among more severely obese patients, who already face an increased risk of recurrence.^{2,12} While a 100-kg patient received, on average, 77% (1380/1800) of the recommended initial continuous infusion, a 175-kg patient received 62% (1965/3150) of the recommended dose.

Few studies have compared recommended vs. actual initial heparin doses in patients with VTE⁶ and we are not aware of any study that has documented the extent of underdosing in obese patients with this condition. A 2005 investigation¹³ that included a national sample of academic, community, and Veterans Administration hospitals compared anticoagulation treatments administered to patients with VTE with the 2001 guidelines of the American College of Chest Physicians that were in effect during the period covered by the study. The investigators reported frequent deviations from the recommended choice of drug for initial therapy, timing of discontinuation, and discharge anticoagulation regimen, but they did not analyze adherence to initial dosing guidelines.

We do not know if our findings would be different in non-obese patients because we limited data gathering to individuals with body mass index ≥ 30 kg/m². Our study focused on this group because we suspected that underdosing would be most pronounced in obese patients. As noted above, the extent of underdosing—that is, the size of the gap between the recommended and actual initial continuous infusion dose—increased with body weight over the range of weights available in our sample of obese patients. If that pattern were to continue in patients with body mass index <30 kg/m², we would expect the problem of underdosing to be less severe in non-obese patients.

In recent years, physicians have shifted from unfractionated to low molecular weight heparin as the standard treatment for VTE, but the former drug is often preferred for certain patients, such as those with renal failure, bleeding disorders, or extremes of obesity.⁵ Since approximately 30% of patients with VTE are obese,^{10,11,13} our findings are applicable to a substantial number of patients.

While we have no reason to believe that residents at our teaching hospital differ from residents elsewhere, we cannot be sure that their prescribing practices are representative. Another limitation of our study is the absence of post-discharge follow-up data that would reveal the incidence of recurrent VTE among study patients treated by these physicians. We know anecdotally that the incidence of recurrences at our institution is very low, but we did not systematically gather recurrence data. Given our limited sample size and the low incidence of recurrence, it would have been difficult to demonstrate a relationship between dose and recurrence risk even if this were a study objective. The incidence of major bleeding complications is also low at our institution (and has been reported elsewhere¹⁴ to be below 5%), so similar remarks apply. That is, demonstrating a relationship between dose and bleeding risk would have been difficult, and tracking such complications was not an objective of the study. It is important to emphasize that the purpose of this study was to compare actual vs. recommended treatments rather than to validate (or dispute) the treatment guidelines. Gathering outcome data to investigate the validity of the guideline would require a different study design.

In conclusion, two key findings from the present study raise serious concerns about treatment with unfractionated heparin in obese patients with VTE. First, a substantial proportion of these patients experienced a delay >24 h in achieving adequate anticoagulation and, second, the vast majority received an inadequate heparin bolus or initial continuous infusion (or both) according to current dosing guidelines. Since obese patients already face an elevated risk of recurrence, it is especially important for physicians to avoid overcautious behavior and, instead, to administer aggressive anticoagulation therapy to help protect these VTE patients from adverse outcomes.

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