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ORIGINAL ARTICLE

The safety of dosing dalteparin based on actual body weight for the treatment of acute venous thromboembolism in obese patients

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Summary. Data evaluating the safety of using weight-based low-molecular-weight heparin in the treatment of obese patients with acute venous thromboembolism are limited. The product monograph of dalteparin suggests the maximum dose should be limited to 18 000 U subcutaneously once daily. There are no specific data regarding the risk of recurrence or bleeding in patients given dalteparin in a weight-based dose of 200 IU kg^{-1}. We report a retrospective chart review of 193 obese patients who weighed more than 90 kg and who received dalteparin at or near to 200 IU kg^{-1} actual body weight for 5–7 days for acute venous thromboembolism with 90 day follow-up information. Of the patients, 77% had idiopathic venous thromboembolism, 16% had an underlying malignancy, and 7% had a transient risk factor. Warfarin was initiated within 2 days with a target International Normalized Ratio range of 2.0–3.0. All patients were followed for 12 weeks post diagnosis. Only two patients had a major hemorrhage, 4 and 8 weeks from diagnosis. This study supports the safety of dosing dalteparin based on actual body weight in obese patients.

Keywords: low-molecular-weight heparin, obesity, treatment, venous thromboembolism.

Introduction

Data evaluating the safety of using weight-based dosing of low-molecular-weight heparin (LMWH) in the treatment of obese patients with acute venous thromboembolism are limited. These patients have often been excluded from randomized trials [1]. In other studies, patients whose weight exceeded the manufacturer's upper limit received the recommended maximum dose, regardless of weight [2]. For dalteparin, this dose is 18 000 IU, which can result in a significant per kilogram dose reduction in obese patients. Studies based on target anti-factor (F)Xa levels suggest that giving the dose according to actual body weight to obese patients achieves similar anti-Xa levels as in non-obese persons [3,4]. It has been our practice to give dalteparin at the full 200 IU kg^{-1} dose (i.e. 200 IU kg^{-1} actual body weight) for patients who weigh more than 90 kg. The purpose of this retrospective study was to determine the rates of major hemorrhage and thromboembolic recurrence for obese (> 90 kg) patients treated for acute venous thromboembolism with dalteparin dose based on actual body weight.

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Patients and methods

In the thrombosis units of our tertiary care centers all patients with acute venous thrombosis are followed until anticoagulant therapy is discontinued. Patients are seen 1 (occasionally 4), 12 and 24 weeks after treatment is initiated and each year thereafter. All suspected bleeding events and recurrence events are investigated and documented. We were therefore able to perform a retrospective chart review and analysis on prospectively collected information. We reviewed our computerized records for patients over 90 kg who were treated for acute deep vein thrombosis (DVT) or pulmonary embolism (PE) as outpatients from May 1996 to July 2003. Patients were primarily referred from the emergency department or directly from their family physician. The diagnosis of venous thromboembolism was objectively confirmed by compression ultrasound, V/Q scan or spiral computed tomography by previously described criteria [5–10]. Patients were included in the study if they weighed > 90 kg. Patients were excluded if they had chronic renal failure requiring dialysis therapy or were known to have a serum creatinine > 200 μmol L^{-1} as suggested by the product monograph. All patients treated in our clinic are enrolled in our database. No patients were excluded on the basis of perceived bleeding risk.

Patients were treated with dalteparin 200 IU kg^{-1} actual body weight subcutaneously once daily or with 100 IU kg^{-1} twice daily for a minimum of 5 days and until the International Normalized Ratio (INR) was > 1.9. Preloaded syringes and multidose vials were used at the physicians' discretion. The first

injection of LMWH was given either in the outpatient clinic or at the emergency room prior to referral, with subsequent doses being administered at home. Where possible, treatment with oral anticoagulation was initiated on the first day, usually with a dose of 10 mg of warfarin. Subsequent dosing of warfarin was adjusted to achieve an INR between 2.0 and 3.0 according to a nomogram with proven efficacy [11]. Treatment with oral anticoagulation continued for a minimum of 3 months and was supervised in our anticoagulation clinics. For the duration of the LMWH therapy, a nurse contacted the patient daily to assess for complications and to communicate the warfarin dose as instructed by the physician. All patients were subsequently assessed in clinic at 1, 4 and 12-week follow-up visits after diagnosis. Patients were asked to report any symptoms or signs of recurrent venous thromboembolism, as well as any bleeding complications.

The primary outcome for this retrospective study was a major hemorrhage in the 3-month follow-up period, although it is likely that bleeding beyond the first 2 weeks of treatment is unrelated to LMWH therapy. A major hemorrhage was defined as one or more of the following: (i) clinically overt bleeding with a drop in hemoglobin of > 20 g L^{-1}; (ii) clinically overt and requiring 2 units or more of packed red cell transfusion; (iii) hemorrhage requiring permanent cessation of anticoagulant therapy; (iv) any retroperitoneal or intracranial hemorrhage.

Secondary outcomes included recurrent venous thromboembolism and death [12,13].

Results

There were 193 patients identified from May 1996 to July 2003 which consisted of 116 (60%) men and 77 (40%) women with an age range of 20–88 years (mean 54 years). All patients weighed more than 90 kg with a mean weight of 114.2 ($\pm$ 18.3) kg (range 91–182 kg). All patients were weighed by the clinic personnel (physician or nurse). The distribution of patient weight is shown in Fig. 1. There were 126 patients (66.5%) with DVT, 55 (28.5%) with PE and 12 (6%) with both DVT and PE. One hundred and forty-eight patients (77%) had idiopathic venous thromboembolism, 31 patients (16%) had an underlying malignancy and 14 patients (7%) had secondary venous thromboembolism.

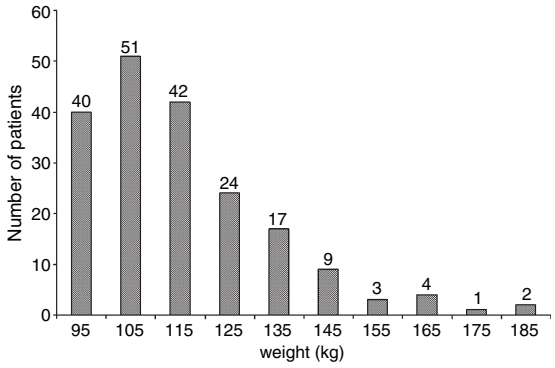

Fig. 1. Histogram demonstrating weight distributions in study patients.

The majority of patients ($n = 151$; 78%) received the recommended daily dose (200 IU kg^{-1} dalteparin) within $\pm$ 5%, for 5–7 days. The majority of patients received once daily dosing. There were 42 patients who received a daily dose of dalteparin < 200 IU kg^{-1} $\pm$ 5% (enabling use of prefilled syringes). All of these patients received a total dose = 18 000 IU daily dalteparin. The mean dose was 21 780 which was on average 191 units kg^{-1}. Details on the dosing according to 10-kg weight increments are outlined in Table 1. Approximately half the patients self-injected (with the other half having the treatment administered by a visiting nurse).

There were no patients who had a major bleed within the first 2 weeks of diagnosis. By the 3-month follow-up, only two patients had a major bleeding event (a lower gastrointestinal bleed and a subdural hematoma at 4 and 8 weeks from diagnosis, respectively) for a bleeding rate of 1.0% [95% confidence interval (CI) 0.1, 3.7). It is unlikely these major bleeding events were due to dalteparin therapy. There was one bleed in the 122 patients on once-daily dosing (0.8%; 95% CI 0.02, 4.5) and one in the 71 patients who received twice-daily dosing (1.4%; 95% CI 0.03, 7.6). Three patients (1.6%, 95% CI 0.3, 4.5) had recurrent venous thromboembolic events in the 3-month follow-up period (one PE at 2 weeks post diagnosis, and two DVTs at 11 weeks post diagnosis). Two recurrences occurred in the 122 once-daily dosing group (1.6%; 95% CI 0.2, 5.8) and one in the 71 twice-daily dosing group (1.4%; 95% CI 0.03, 7.6). No patient died within the 3-month follow-up.

Discussion

The reported clinical experience with LMWH for the treatment of acute venous thromboembolism in persons > 90 kg (many of whom are obese) has been limited. These patients have typically been excluded from randomized studies or had their dose limited to a maximum as outlined in the product monograph [1,2]. In our study, we reported the successful outpatient treatment of 193 consecutive patients > 90 kg with acute venous thromboembolism, with dalteparin administered at, or near, an intended dose of 200 IU kg^{-1} actual body weight for 5–7 days with concomitant warfarin therapy continued for a minimum of 3 months. Only two of 193

Table 1 Dosing information by weight categories in increments of 10 kg

Weight (kg)	*N*	Mean dose (SD)	No. full dose $\pm$ 5%	No. OD dosing	No. BID dosing
90–99	40	19300 (814)	39	24	16
100–109	52	20850 (693)	49	35	17
110–119	41	21470 (1746)	21	26	15
120–129	25	24300 (2046)	22	16	9
130–139	16	25250 (2200)	8	10	6
140–149	9	26920 (3900)	6	5	4
> 150	10	28280 (4800)	6	6	4

N, Number of patients per category; SD, standard deviation; OD, once daily; BID, twice daily.

patients had a major hemorrhage (lower gastrointestinal and a subdural hematoma) at 4 and 8 weeks post diagnosis of venous thromboembolism, respectively. Hence, these bleeding events were unlikely to be due to dalteparin therapy. This bleeding rate is similar to rates previously reported in all patients of all weights from our centers, suggesting that a full dose of dalteparin does not increase the risk of major bleeding [12]. Due to the small numbers of patients studied we cannot comment on the relative safety and efficacy of once vs. twice-daily dosing in these patients.

Our study provides evidence that it is safe to dose LMWH in patients based on their actual weight. These data support the results of previous studies measuring anti-Xa levels that suggested full per weight dosing achieves similar LMWH anti-Xa levels as non-obese persons [3,4]. Wilson and colleagues showed that body mass does not have a significant effect on the response to LMWH up to a weight of 190 kg in patients with normal or near normal renal function. The anti-Xa levels in their patient population were similar to non-obese patients (i.e. mean trough and peak anti-Xa levels on day 3 were 0.12 and 1.01 IU mL^{-1} and 0.11 and 1.12 IU mL^{-1} for non-obese and obese patients, respectively). These levels are all within the manufacturer's recommended range for once-daily dosing of dalteparin (trough < 0.3 U mL^{-1} and peak < 1.7 U mL^{-1}) [3]. A similar observation was made by Sanderink *et al.*, who showed that enoxaparin was well tolerated in both obese and non-obese volunteers when administered subcutaneously [4]. Subcutaneous enoxaparin administration yielded similar levels of LMWH in obese and non-obese volunteers, and steady state for anti-Xa and anti-factor IIa activities was reached at similar times.

If full per weight dosing in obese individuals does not lead to increased anti-Xa levels as previous studies suggest, and does not lead to an increased risk of bleeding as our study suggests, then limiting these patients to a maximum daily dose of 200 IU kg^{-1} could be considered 'under-dosing'. This could potentially lead to an increased risk of recurrent venous thromboembolism. No studies to date have assessed this possibility.

The main limitation of our study is its retrospective nature; however, all patients were treated prospectively according to a standardized protocol, information on adverse events was collected in all patients prospectively, and no patients were lost to follow-up. We did not measure anti-Xa levels since we used an outpatient population and assessment of anti-Xa levels would have been impractical.

Our study suggests that it is safe to administer dalteparin at or near full dose based on actual body weight for the treatment of acute venous thromboembolism without an increased risk of major hemorrhage. Limiting the dose of dalteparin to 18 000 IU could lead to an increased risk of recurrence of venous thromboembolism. Randomized studies would be required to assess this risk.

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