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Therapeutic Enoxaparin in the Morbidly Obese Patient: A Case Report and Review of the Literature

Claudia M. Hanni[1], Sheila M. Wilhelm[2,3], Bianca Korkis[2,3], Elizabeth A. Petrovitch[3], Kanella V. Tsilimingras[3], and Sean M. McConachie[2,4]

Abstract

Enoxaparin is a low molecular weight heparin commonly used in the treatment of venous thromboembolisms (VTEs); however, evidence on optimal empiric dosing recommendations are lacking in patients with morbid obesity. Utilization of an absolute dose cap, anti-Xa monitoring, and reduced empiric dosing are among the techniques used in this population. We describe a case of a morbidly obese man (body-mass index, BMI: 68.2 kg/m^2, total body weight: 236 kg) who required therapeutic enoxaparin for suspected pulmonary embolism (PE) and critical limb ischemia as a bridge therapy during warfarin initiation. An initial empiric dose of 200 mg Q12 hours (0.85 mg/kg) resulted in an anti-Xa level of 1.01 IU/mL following the fifth dose, and no dose modification was deemed necessary. He experienced no adverse effects from treatment. This report adds to a growing body of evidence illustrating the need for reduced empiric weight-based doses of enoxaparin in the morbidly obese population and raises the question of whether dose capping is an appropriate practice in the clinical setting of morbidly obese patients with acute VTE.

Keywords
anticoagulants, pharmacokinetics, cardiovascular

Introduction

Obesity has reached epidemic proportions in the United States and is considered a major public health problem. Recent studies suggest that up to 1 in 3 adult Americans are obese (BMI $\geqslant$ 30 kg/m^2).[1] Additionally, 7.7% of patients are considered morbidly obese (BMI $\geqslant$ 40 kg/m^2), a 70% increase from 2000 to 2010.[2,3] Obesity predisposes individuals to a number of adverse health conditions including venous thromboembolism (VTE).[4,5] Although obese patients are at a disproportionately high-risk for both deep vein thrombosis (DVT) and pulmonary embolism (PE), they are underrepresented in pharmacokinetic (PK), pharmacodynamic (PD), and clinical trials that lead to anticoagulant medication approval.[4] This often leaves clinicians little choice but to rely on PK data and case reports to inform their prescribing and dosing decisions in morbidly obese individuals.

Enoxaparin is a low molecular weight heparin (LMWH) recommended for the treatment of VTE.[5] Despite widespread use, controversy remains as to the appropriate dosing recommendations for patients with morbid obesity. The Food and Drug Administration (FDA)-approved dosing recommendation for VTE is 1 mg/kg using total body weight (TBW) for all patients;[6] however, PD parameters are known to vary with body size.[7] In early PK/PD studies, it was demonstrated that undersized patients (BMI $\leqslant$ 18.5 kg/m^2) required lower enoxaparin doses on a mg/kg basis to attain goal anti-Xa levels as compared to normal weight controls, and overweight patients required higher doses.[6] Additionally, recent cohort data suggest that in morbidly obese patients (BMI $\geqslant$ 40 kg/m^2), reduced weight-based doses produce therapeutic anti-Xa levels more reliably than 1 mg/kg dosing regimens.[8,9] Due to the lack of sufficient evidence, many practitioners advocate for anti-Xa monitoring in patients with obesity,[10,11] while others recommend a "dose cap" strategy.[12]

Herein, we report a case of a morbidly obese patient (body-mass index, BMI: 68.2 kg/m^2) with suspected PE and limb ischemia who was bridged to warfarin using therapeutic

[1]Beaumont Hospital, Royal Oak, MI, USA
[2]Wayne State University, Detroit, MI, USA
[3]Harper University Hospital, Detroit, MI, USA
[4]Beaumont Hospital, Dearborn, MI, USA

Corresponding Author:
Sean M. McConachie, Assistant Professor (Clinical), Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, 259 Mack Ave, Detroit, MI 48201, USA.
Email: Sean.McConachie@wayne.edu

dose enoxaparin. Published literature regarding therapeutic enoxaparin in morbidly obese individuals with VTE is also reviewed.

Case Report

A 52-year-old African American, morbidly obese man (height: 183 cm, weight: 236 kg, BMI: 68.2 kg/m^2) presented to the hospital with a chief complaint of left lower extremity pain and shortness of breath with exertion. His past medical history was significant for hypertension, bilateral lower extremity lymphedema and chronic back pain. He stated his lower extremity pain was a chronic issue that worsened with exertion and his dyspnea had been occurring for 4 weeks and was associated with orthopnea. Prior to admission, his medications included the following: aspirin 81 mg daily, atorvastatin 40 mg daily at bedtime, metoprolol tartrate 50 mg twice a day, and duloxetine ER 60 mg daily.

On admission, his laboratory values included the following: sodium 134 mEq/L, potassium 3.5 mEq/L, blood urea nitrogen 18 mg/dL, serum creatinine 1.96 mg/dL (baseline 1.1-1.3 mg/dL), glucose 228 mg/dL, and elevated d-dimer 8.84 mg/L FEU. Coagulation laboratory values at baseline included the following: hemoglobin 13 g/dL, hematocrit 40.5%, platelets 234 $\times$ 10^3/μL, aPTT 24.2 seconds, PT 11.3 seconds, International normalized ratio (INR) 1.05. Vitals demonstrated tachycardia (heart rate: 134 bpm), normal respiratory rate (18 RR), blood pressure (135/83 mmHg), and temperature (37.6°C). Ultrasound examination of the left lower extremity was limited by edema; however, no thrombus was identified. A ventilation and perfusion scan performed for suspected PE was severely limited by body habitus, but revealed low probability for PE in the areas that were able to be visualized. CT scan was unable to be performed even after patient's renal function recovered to baseline due to his body habitus. The medical team deemed the patient at moderate risk of PE given his clinical picture which included ongoing tachycardia despite beta blockade, elevated d-dimer, and poor discriminative value of diagnostic tests. An ankle brachial index was then performed on the patient's left leg revealing a value of 0.0, indicating critical limb ischemia. Angiography of the leg demonstrated complete lack of flow below the knee; however, the vascular surgeon recommended against thrombectomy and thrombolytics given the patient's body habitus and clinical condition. The decision was made to forego surgical intervention and pursue systemic anticoagulation, which was already deemed necessary for suspected PE.

Intravenous heparin therapy titrated to a target PTT of 48-78 seconds based on institutional protocol was initiated for both acute limb ischemia and suspected PE with concomitant warfarin until INR equaled or exceeded 2 on two consecutive days. On day 3 of warfarin therapy, the medical team transitioned the patient from heparin to subcutaneous (SQ) enoxaparin to expedite discharge to skilled nursing facility (Table 1). A weight-based dose of enoxaparin 0.83 mg/kg SQ Q12 hours was chosen based on previously published literature[8] and rounded to 200 mg SQ Q12 hours based on institutional policy, resulting in a dose of 0.85 mg/kg SQ Q12 hours. Anti-Xa levels were ordered following the third dose; however, due to an error anti-Xa levels were rescheduled and drawn 4 hours following the fifth dose of enoxaparin, which resulted in 1.01 IU/mL. The institutional target therapeutic range for enoxaparin anti-Xa is 0.5-1 IU/mL. Enoxaparin therapy of 200 mg SQ Q12 hours was continued. The patient was discharged to a skilled nursing facility on day 6 of warfarin therapy with an INR of 2.17, and with improved lower extremity pain and swelling. He was discharged on his home medications plus warfarin 10 mg daily and enoxaparin 200 mg SQ Q12 hours. On day 7 of warfarin therapy, the INR value was 2.2. Enoxaparin therapy was discontinued since patient had achieved an INR $\geq$ 2 on two consecutive days. Of note, all other laboratory values including coagulation panel remained within normal limits, and patient did not exhibit any signs or symptoms of bleeding during therapy.

Discussion

This patient case adds to the growing amount of published evidence demonstrating reduced weight-based doses of therapeutic enoxaparin may be necessary for the morbidly obese population. The nonlinear increase in PD effects with increasing body weight has a physiologic basis. Enoxaparin is a hydrophilic molecule with a volume of distribution (V_d) that roughly approximates plasma volume.[6-8,13] Blood volume and total body water, however, do not increase linearly with increasing body weight.[14] Therefore, an argument for a reduced dose requirement of enoxaparin could be made for the morbidly obese population; however, there is limited PK data to support this conclusion.

One PK/PD analysis compared 24 healthy obese patients (BMI range: 29.6-48.4 kg/m^2) and 25 normal weight individuals (BMI range: 19.4-25.5 kg/m^2) who were administered 2 separate enoxaparin regimens separated by a 7-day washout period: 1.5 mg/kg SQ once daily for 4 consecutive days followed by 1.5 mg/kg IV infusion over 6 hours.[7] In the analysis of SQ enoxaparin, it was found that obese patients took longer to reach steady state concentrations when compared to normal weight individuals and obese patients also had higher exposure in terms of anti-Xa activity (14% higher on day 1, $P = 0.006$; 19% higher on day 4, $P = 0.001$). In the analysis of IV enoxaparin, obese individuals had higher overall clearance (Cl) and V_d ($p < 0.01$); however, they had a lower weight-based Cl and V_d. The authors concluded that overall exposure is higher in obese patients when treated with similar weight-based dosing regimens. However, an analysis by Bazinet et al. which assessed the difference in PD response to therapeutic dose enoxaparin between obese (BMI $\geq$ 30 kg/m^2) and nonobese individuals was unable to

corroborate these earlier findings.[15] The authors identified higher peak anti-Xa levels among obese individuals in both Q24 and Q12 dosing regimens, but the results were not significant. This analysis was limited by a low total number of obese patients (n = 30) and the fact that morbidly obese patients were not identified. Additionally, a PK analysis in patients receiving dalteparin demonstrated a nonsignificant difference in mean peak anti-Xa levels between heavier patients and normal weight patients (1.12 vs. 1.01 IU/mL). Although patients were not stratified based on BMI and the overall number of patients at least 40% above their IBW was small (n = 10), the trial did include one patient with TBW of 190 kg (BMI 58 kg/m^2).[16] Extrapolation of these findings to the morbidly obese population should be done cautiously as these studies are limited by inconsistencies in defining overweight patients, lack of identification of morbidly obese patients, small sample sizes (30 patients and 10 patients, respectively), and lack of concrete clinical outcomes.

Clinical trial data among patients on enoxaparin also have not demonstrated significant differences in clinical outcomes between obese and nonobese patients. Post hoc analysis of the Matisse trials indicated that weight-based enoxaparin dosing in obese patients (BMI $\geqslant$ 30 kg/m^2) was as safe and effective as in nonobese patients[17] and analysis of the prospective registry of patients with venous thromboembolism (RIETE) trial also failed to find statistically significant differences in safety or efficacy data between heavier patients (>100 kg) and normal weight patients treated with heparin or enoxaparin.[18] Questions remain regarding the morbidly obese population as they were not identified and analyzed separately in these studies. In addition, studies show that many institutions do not dose enoxaparin for obese patients based on FDA-approved labeling recommendations.[19,20]

ITo identify all studies on the use of therapeutic enoxaparin in morbidly obese patients with VTE a literature search of the PubMed database was conducted using the search terms "enoxaparin" and "obesity" from inception through May 15, 2018. Abstracts were reviewed for pertinent articles. Studies pertaining to DVT prophylaxis or for other non-VTE indications were excluded. In total, 5 cohort studies and 2 case reports were identified (Table 2).

Deal et al. performed a single center retrospective review of all morbidly obese patients prescribed therapeutic enoxaparin with evaluable anti-Xa levels from 2004 to 2010.[9] Of the 26 patients identified, mean BMI was 49.5 kg/m^2 (range: 48.1-98.1), 17 patients received enoxaparin for acute VTE, and median duration of therapy was 4 days. The most common initial dose was 0.8mg/kg SQ Q12 hours, however, 2 individuals (weight 140 and 144kg) were initiated on 1 mg/kg dosing. Goal steady state anti-Xa levels (0.5-1.0 IU/mL) were achieved in 12 patients (46%), while anti-Xa levels were supratherapeutic in 10 patients (38%) and uninterpretable in 4 patients (15%). A total of 6 bleeding events occurred, which were more commonly detected in patients with supratherapeutic anti-Xa levels than those who were at goal (40% vs. 0%; P = 0.033). Anti-Xa levels were higher in those that bled as opposed to those who did not bleed (1.5 IU/mL vs. 0.98 IU/mL; p=0.07). No thrombotic events occurred. Attainment of therapeutic anti-Xa levels did not differ based on renal function, total weight, BMI, or initial dose.

Based on the results of this study, Lalama et al. developed an institutional protocol for reduced initial enoxaparin doses (0.75 mg/kg) in patients with BMI $\geqslant$ 40 kg/m^2 or weight $\geqslant$ 200 kg.[21] The authors performed a 1-year retrospective cohort study which assessed 31 patients over a 13-month period who received enoxaparin 0.75 mg/kg and had evaluable peak anti-Xa levels. The average TBW of the cohort was 138 kg (range: 105-197 kg) and average BMI of 46.2 kg/m^2 (range: 40.2-62 kg/m^2). The majority received enoxaparin for VTE (65%) and for an average duration of 4.8 days. Initial therapeutic peak anti-Xa level (0.6-1.0 IU/mL) was achieved in 15 patients (48%). Of those who did not achieve therapeutic levels, 11 patients (36%) had supratherapeutic anti-Xa levels and 5 patients had subtherapeutic levels (16%). Overall, the average dose to achieve a goal anti-Xa level during hospital admission was 0.71 mg/kg twice daily. In a post hoc analysis study authors found that age >50 years was associated with an increased incidence of supratherapeutic anti-Xa compared to younger patients (43% vs. 20%; P = 0.03). In terms of clinical outcomes, 2 episodes of bleeding occurred and one VTE occurred.

A third retrospective cohort study conducted by Lee et al. analyzed morbidly obese patients (BMI $\geqslant$ 40 kg/m^2 or TBW $\geqslant$ 150 kg) who received therapeutic enoxaparin at an unadjusted dose of 1 mg/kg SQ Q12 hours (or Q24 hours in patients with CrCl < 30 mL/min) for at least 3 days and had evaluable anti-Xa levels.[10] Of the 99 enrolled patients, the average BMI was 50.6 kg/m^2 (range: 40-95.1 kg/m^2); 37% were treated for VTE, 36% for acute coronary syndrome, and 27% for atrial fibrillation. Overall, only 35 patients (35.4%) achieved therapeutic anti-Xa levels (0.5-1.1 IU/mL), whereas 50 patients (50.5%) had supratherapeutic levels and 14 patients (14.1%) had subtherapeutic levels. Interestingly, renal dysfunction (CrCl < 30 mL/min) was independently associated with subtherapeutic anti-Xa levels, possibly indicating that 1 mg/kg Q24 hours may be inadequate for obese patients, even with renal dysfunction. The authors concluded that anti-Xa monitoring is appropriate in obese patients; however, no indication was made as to whether empiric 1 mg/kg dose strategies were to change based on the low rate of therapeutic anti-Xa levels.

Hagopian et al. performed a single-center retrospective analysis comparing bleeding rates in morbidly obese patients.[22] Over the 6-month inclusion period, 100 morbidly obese patients on therapeutic enoxaparin for at least 24 hours were compared to 200 control patients with BMI $\leqslant$ 40 kg/m^2. At baseline, the morbidly obese patients were more likely to be female (75% vs. 56%; P < 0.01), younger (Average 50.3 years vs. 57.6 years; P < 0.01), have hypertension (63% vs. 47%; P = 0.01), diabetes mellitus (39% vs. 21%;

$P < 0.01$), and factor V deficiency (4% vs. 0%; $P = 0.01$). Indication for anticoagulation and duration of enoxaparin therapy was similar between subgroups; however, morbidly obese patients had lower initial (0.96 vs. 1.05 mg/kg; $P < 0.01$) and final doses (0.98 vs. 1.04 mg/kg; $P < 0.01$) compared to the control group. Overall, there was no difference in bleeding endpoints between groups ($p > 0.05$ for all analyses). In a multivariate analysis of risk factors for bleeding, authors found that female gender (adjusted odds ratio (AOR): 2.05; $P = 0.02$), enoxaparin dose < 0.9 mg/kg (AOR: 2.35; $P = 0.04$), and duration of enoxaparin use > 48 hrs (AOR 2.42; $P < 0.01$) were associated with an increased risk of bleeding, whereas concomitant warfarin administration was associated with a decreased risk of bleeding (AOR 0.46; $P < 0.01$). Following study completion, the authors concluded that weight-based enoxaparin dosing with a dose cap of 150 mg could be safe in the morbidly obese group as the highest dose administered in the study was 150 mg.

Finally, one prospective observational cohort study has been conducted to determine the enoxaparin dose required to achieve therapeutic anti-Xa levels in morbidly obese patients (BMI $\geqslant$ 40 kg/m^2 or TBW $\geqslant$ 140 kg).[8] A total of 41 patients were enrolled with a median BMI of 45.6 kg/m^2 (range: 36.8-92.1), median TBW of 138.1 kg (range: 95.3-266.7), and median enoxaparin treatment duration of 3 days. The median dose required for therapeutic steady state anti-Xa levels was significantly lower compared to the median dose of patients with supratherapeutic levels (0.83 mg/kg vs. 0.98 mg/kg; $P = 0.02$). Univariable analysis revealed that patients with higher initial doses based on TBW were more likely to have a supratherapeutic anti-Xa level (OR 0.21 for <0.95 mg/kg dosing versus $\geqslant$ 0.95 mg/kg dosing [95% CI: 0.05-0.84, $P = .02$]). Additionally, in an analysis of PK parameters, patients with TBW > 140 kg had higher median V_d (2.5 vs. 3.7 L; $P = 0.03$); however, weight-based V_d was not significantly different (0.023 vs. 0.020 L/kg; $P = 0.41$). There was an overall bleeding rate of 19.5% in the cohort, with one event classified as a major bleed. Patients who experienced bleeding were taking more concomitant anticoagulants and had a higher proportion of supratherapeutic anti-Xa levels (26.1% vs. 11%). These differences were not statistically significant; however, the small sample size of the study may have lacked adequate power to detect a true difference.

Additionally, 2 recent case reports also described the need for reduced empiric enoxaparin doses in morbidly obese patients.[23,24] A morbidly obese (BMI: 114 kg/m^2, TBW: 322 kg), 22-year-old female patient with a suspected PE was initiated on enoxaparin 160 mg Q12 hours (~0.5 mg/kg) based on an institutional dose capping protocol.[23] The patient's initial peak anti-Xa level was subtherapeutic following the fourth dose (0.4 IU/mL, goal 0.5-1.1), so the dose was empirically increased by 25% to enoxaparin 200 mg Q12 hours (0.62 mg/kg), which resulted in a therapeutic anti-Xa level (0.78 IU/mL) on hospital day 4. She was discharged on this dose as bridge to warfarin therapy. Another case detailed a 52-year-old, morbidly obese male (BMI: 61 kg/m^2, TBW: 210 kg) who presented with an acute MI who was initiated on enoxaparin 140 mg SQ Q12 hours (0.67 mg/kg).[24] The initial peak anti-Xa level following the third dose was subtherapeutic (0.37 IU/mL). The patient required 2 additional dose increases to attain therapeutic peak anti-Xa levels (0.84 IU/mL) on an enoxaparin dose of 180 mg Q12 hours (0.85 mg/kg). Neither patient demonstrated adverse effects.[23,24]

Taken together, recently published data indicate supratherapeutic anti-Xa levels occur 40% to 50% of the time based on empiric dosing regimens (both 1 mg/kg and lower doses),[9,10,21] and a delay in achieving therapeutic anti-Xa levels when dose capping is applied in this population.[23,24] Our patient was dosed based on previously published evidence suggesting a dose of 0.83 mg/kg may provide the most appropriate empiric dose regimen in morbidly obese patients.[8] Although the anti-Xa level was outside the therapeutic range by 0.01 IU/mL, the decision was made to continue at the same dose given the proximity to the therapeutic range, lack of negative safety outcomes, and an INR that was close to target therapeutic range at the time of the level.

Although there are a growing number of anticoagulant medications available for use in patients with acute VTE, limited real-world data of the direct oral anticoagulants (DOACs) in morbidly obese patients may lead to a continued reliance on warfarin for treatment of VTE in this population.[25] Indeed, recent recommendations from the Internal Society of Thrombosis and Hemostasis do not recommend DOACs in patients with BMI $\geqslant$ 40 kg/m^2 or TBW $\geqslant$ 120 kg due to lack of evidence.[25] In terms of bridging medications, unfractionated heparin has several advantages over LMWHs for morbidly obese patients with acute VTE including rapid monitoring of therapeutic efficacy, ease of titration, and lack of required dose adjustments for renal impairment.[11] However, the need for continuous IV access and inconsistent PK profile are problematic in patients who are otherwise ready for discharge. Enoxaparin, however, has a more reliable PK profile compared to heparin and may be ideal for expedition of discharge in patients being bridged to warfarin. Current American College of Chest Physician (ACCP) guidelines do recommend anti-Xa monitoring in the setting of obesity.[11] However, anti-Xa levels are not monitored until steady state, leaving a window of 36 to 60 hours in which the therapeutic effects of enoxaparin are unknown. Similar to existing studies, this report only addresses enoxaparin dosing in the acute setting. Further studies are needed to determine the safety and efficacy of enoxaparin dose adjustment in morbidly obese patients requiring prolonged therapy.

The costs of hospitalization have been estimated to make up 50% of the total cost of medical care for patients admitted with acute VTE.[26] One economic analysis found that the costs of the first 3 days of hospitalization are particularly high, and interventions designed to reduce length of stay may result in significant cost savings.[27] The ability to safely transition patients to enoxaparin for expedited discharge is

Table 1. Anticoagulant Dosing by Hospital Day.

Treatment day	INR	Warfarin dose (mg)	Bridge therapy	Lab monitoring
1	1.08	10	Heparin IV 2600 units/hr	aPTT = 37.2 sec
2	1.1	10	Heparin IV 2800 units/hr	aPTT = 57.8 sec
3	1.24	7.5	Enoxaparin SQ 200 mg every 12 hr	
4	1.50	10	Enoxaparin SQ 200 mg every 12 hr	
5	1.71	10	Enoxaparin SQ 200 mg every 12 hr	
6	2.17	10	Enoxaparin SQ 200 mg every 12 hr	Anti-Xa = 1.01 IU/mL
7[a]	2.2	10	Enoxaparin SQ 200 mg every 12 hr	

Note. INR = International normalized ratio; IV = Intravenous; SQ = Subcutaneous; aPTT = Activated partial thromboplastin time; Sec = seconds; Hr = hours.
[a]Enoxaparin was discontinued on day 7 of treatment

Table 2. Studies Assessing Therapeutic Enoxaparin for VTE in Morbidly Obese Patients.

Citation	Study design, (*n*)	Population	Enoxaparin	Clinical outcomes/results
Thompson-Moore[8]	Prospective observational cohort (41)	• Median BMI: 45.6 kg/m^2 (36.8-92.1) • Median weight: 138.1 kg (95.3-266.7) • Age (years, mean): 55.9 • Male gender: 48.8%	• Dosing: • 0.90 mg/kg (range: 0.83-1.04) • Maximum dose: 160 mg • Goal anti-Xa level: • 0.6 to 1.0 IU/mL	• 38.9% achieved goal anti-Xa levels • Enoxaparin median doses: • Goal anti-Xa level: 0.83 mg/kg • Above target anti-Xa: 0.98 mg/kg • No difference in bleeding or thrombotic events
Deal[9]	Retrospective cohort (26)	• Median BMI 49.5 kg/m^2 (40.1-98.1) • Median weight: 162 kg (106-243) • Age (years, median): 45 • Male gender: 46% • VTE indication: 73%	• Dosing • Median: 0.8 mg/kg Q12 hours • Range: 0.5-1.1 mg/kg • Goal anti-Xa level: • 0.5 to 1.1 IU/mL	• 46% achieved goal anti-Xa levels • Above target anti-Xa: 38% • Uninterpretable: 15% • Overall 6 bleeding events occurred • More common in above target group (40% vs. 0%; p=0.033)
Lee[10]	Retrospective cohort (99)	• Mean BMI: 50.6 kg/m^2 (40-95.1) • Mean weight: 146.3 kg (78-249) • Age (years, mean): 57.8 • Male gender: 45% • VTE indication: 37%	• Dosing: • 1.5 mg/kg Q12 • Or 1 mg/kg Q24 • Goal anti-Xa level: • 0.5 to 1.1 IU/mL	• 35.4% achieved goal anti-Xa levels • Above target anti-Xa: 50.5% • Below target anti-Xa: 14.1% • No bleeding events occurred
Lalama[16,21]	Retrospective cohort (31)	• Median BMI 46.2 kg/m^2 (40.2-62) • Median weight: 138 kg (105-197) • Age (years, median): 61 • Male gender: 48% • VTE indication: 65%	• Dosing: • 0.75 mg/kg Q12 hours • Goal anti-Xa level: • 0.6 to 1.1 IU/mL	• 48% achieved goal anti-Xa levels • Above target anti-Xa: 36% • Below target anti-Xa: 16% • Two minor bleeding events reported
Hagopian[17,22]	Retrospective case-control (300)	• BMI: ⩾40 kg/m^2 (n): 100 • Max weight: 175.5 kg • Age (years, mean): 50.3 • Male gender: 25%	• Dosing: • ⩾ 0.85 mg/kg Q24 hours or Q12 hours • Maximum dose: 150 mg • Goal anti-Xa level: • Once daily: 1-2 IU/mL • Twice daily: 0.5-1 IU/mL	• Anti-Xa levels not routinely obtained in study • No difference in bleeding events (p = 0.30) • Morbidly obese bleeding events: 29% • Control group bleeding events: 23.5%
Heitlage[23]	Case Report	• 22 y/o female • BMI: 114 kg/m^2 • Total weight: 322 kg • Suspected PE	• Initial Dosing: • 160 mg BID • Max dose based on institution • Goal anti-Xa level: • 0.5 to 1.1 IU/mL	• Initial anti-Xa level low (0.4 IU/mL) • Enoxaparin dose for goal anti-Xa level: • 0.62 mg/kg Q12 hours • Dose adjustments required: 1 • No adverse events reported
Mazhar[24]	Case Report	• 52 y/o male • BMI: 61 kg/m^2 • Total weight: 210 kg • Lower extremity DVT	• Initial Dosing: • 140 mg Q12 hours (0.67 mg/kg) • Goal anti-Xa level: • 0.5 to 1.0 IU/mL	• Initial anti-Xa level low (0.37 IU/mL) • Enoxaparin dose for goal anti-Xa level: • 0.86 mg/kg Q12 hours • Dose adjustments required: 2 • No adverse events reported

Note. QD = daily; BID = twice daily; BMI = body mass index; VTE = venous thromboembolism; Y/o = "year old"; DVT = deep vein thrombosis.

therefore an attractive option; however, evidence regarding the optimal empiric dosing regimen for morbidly obese patients is unclear, so prolonged hospitalization for anti-Xa monitoring is still required by our institution. Published evidence demonstrates a discrepancy between institutions and practitioners as to whether weight-based dosing or "dose capping" occurs.[9,10,21,23,24] Studies demonstrate that morbidly obese patients have high rates of supratherapeutic anti-Xa

levels, even at reduced initial doses.[9,10,21] However, reliance on anti-Xa data as a surrogate endpoint is also limited by factors including lack of inter-laboratory agreement on levels and lack of rigorous clinical data to justify the suggested anti-Xa target ranges.[28]

Until further data emerge regarding empiric enoxaparin dosing regimens in the morbidly obese population with acute VTE, institutions will have to determine whether absolute dose capping, reduced empiric weight-based regimens, or a combination of approaches is most appropriate. ACCP recommendations for anti-Xa monitoring should still be followed.[11] One consistent thread that has emerged through recent data and case reports is the fact that morbidly obese patients often require less than the routinely recommended empiric therapeutic enoxaparin dosing of 1 mg/kg to achieve anti-Xa levels within the accepted therapeutic range; however, further studies are needed to determine the optimal empiric dose in morbidly obese patients and which specific patients should receive dose reduction.

Conclusion

Therapeutic dose enoxaparin was used successfully in a morbidly obese patient at a weight-based dose of 0.85 mg/kg SQ Q12 hours without the need for further adjustment. This case provides additional evidence that reduced empiric dosing may be an appropriate dosing strategy in the morbidly obese population for the treatment of VTE.

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ORCID iDs

Sheila M. Wilhelm https://orcid.org/0000-0002-7045-6690

Sean M. McConachie https://orcid.org/0000-0003-4889-7307

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