REVIEW

Anticoagulation with Enoxaparin in Patients with Obesity

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Abstract

Obesity is a relatively common characteristic in modern western world populations and has a significant impact on the person's health status. Despite the fact that it constitutes a well-described risk factor for thromboembolic events, the optimal anticoagulation strategy in obese patients remains vague. The available data suggest that while standard fixed enoxaparin doses (for prophylactic purposes) can lead to subtherapeutic effect, the conventional weight-based dosing schemes may result in overtreatment. Although not particularly strong, contemporary evidence indicate that a dose reduction in morbidly obese patients will likely result in a therapeutic anti-Xa level without an increased probability for bleeding or VTE. ***Rhythmos 2021;16(2):34-38.***

Keywords: obesity; anticoagulation; low molecular weight heparins; heparin; thromboembolism

Abbreviations: ABW = adjusted body weight; BMI = body mass index; GFR = glomerular filtration rate; IBW = ideal body weight; LBW = lean body weight; LMWHs = low-molecular-weight heparins; PNWT = predicted normal weight; VTE = venous thromboembolism

Introduction

Obesity is defined as a body mass index (BMI) of ≥30 kg/m^2 and is increasing in prevalence during the past decades.[1] In 2016, 650 million people worldwide were considered to have obesity, a number comprising 13% of adults.[1] Traditionally, obesity is classified into class I (BMI 30–34.9 kg/m^2), class II (35–39.9 kg/m^2), and class III (≥40 kg/m^2) or extreme/morbid obesity.[2] Despite obesity being a well-described risk factor for venous thromboembolism (VTE), [3] the optimal anticoagulation in this population group, in particular in individuals with class III obesity, remains unclear. Obesity has a variable influence on drug pharmacokinetics[4] modifying in particular the volume of distribution and probably the hepatic and renal clearance. Anticoagulants are very widely used and the difficulty of choosing the correct dosage in patients with obesity is an issue largely encountered in everyday practice. In this brief review, we present the current evidence on the management of this population regarding the administration of anticoagulant therapy.

Pharmacokinetics

In order to discuss the effect of obesity on drug distribution and elimination, we should first determine some key terms. Ideal body weight (IBW) is calculated by the formula:

IBW (kg) = 45.4 kg (49.9 kg if male) + 0.89 x (height in cm-152.4)

This calculation does not take into account the body composition since all patients of the same sex and height would have the same IBW. Adjusted body weight (ABW):

ABW = IBW + 0.4 x (ABW - IBW)

which adds some proportion of the difference between the total body weight and the ideal body weight has been proposed to overcome this flaw, and this metric is frequently used for aminoglycoside dose calculation.

Lean body weight (LBW) LBW describes weight devoid of almost all adipose tissue. The most commonly used formulas to calculate it are:

LBW(kg) = 1.10 x TBW- 0.0128 x BMI x TBW (males)
and
LBW (kg) = 1.07 x TBW- 0.0148 x BMI x TBW (females)

However, results may be inaccurate at extreme height or weight, and thus other approaches have also been described. [5] Predicted normal weight (PNWT) is used to predict the expected normal weight of an overweight or obese individual. PNWT equals the sum of the LBW plus a fraction of the individual's excess fat content that represents predicted normal fat mass. PNWT is calculated as follows:

PNWT(kg) = 1.57 x TBW- 0.0183 x BMI x TBW- 10.5 (males), and

PNWT (kg) = 1.75 x TBW - 0.0242 x BMI x TBW - 12.6 (females)

This metric was designed for pharmacokinetic purposes, but it will not perform ideally at extreme weights or heights as it derives from the conventional, older equations for LBW. [6]

The volume of distribution of a drug can differ between individuals with obesity and normal weight individuals, but these changes are drug-specific and can be attributed to the physicochemical properties of each drug. [4] The clearance of a drug is largely determined by physiological processes, such as liver and kidney function,

which may be altered in the individuals with obesity. Obesity has been linked to nonalcoholic fatty liver disease, and the accumulation of fat in the liver of individuals with obesity may alter hepatic blood flow. [7,8] However, the effect of obesity on liver function and renal procedures such as glomerular filtration, tubular secretion and tubular reabsorption is unclear. Consequently, no weight descriptor exists to characterize drug clearance in patients with obesity. [4] Elimination half-time, which is a function of the two former parameters (volume of distribution and clearance), may also change in persons with obesity in an unpredictable way.

Among parenteral anticoagulants, low-molecular-weight heparins (LMWHs) are most commonly used, because of their more predictable bioavailability and anticoagulant effects, compared to unfractionated heparin. [9] The appropriate dosage in patients with obesity, however, is an issue frequently encountered in clinical practice. In a study of 48 patients with mean BMI 22.4 (n=24) and 34.8 (n=24) kg/m^2, subcutaneous and intravenous enoxaparin was administered at a dose of 1.5 mg/kg TBW. [10] Mean area under the plasma activity-time curve from time zero to infinity for anti- Xa activity was statistically greater in subjects with obesity, as was the time to reach maximum concentration, suggesting a lower rate of absorption. Intravenous infusion over 6 hours resulted in an increased maximum activity and area under the plasma activity-time curve for anti-Xa activity in the cohort with obesity. Clearance and volume of distribution at the equilibrium (steady-state), when normalized to TBW, were lower in the participants with obesity, a finding indicating that TBW might not be the metric of choice to calculate weight-based doses of enoxaparin. [10] In a pharmacokinetic-pharmacodynamic modelling study in 96 patients with BMIs ranging from 15 to 45 kg/m^2, LBW emerged as a key covariate for enoxaparin clearance. [11]

On the other hand, Bazinet et al.[12] compared anti-Xa activity in hospitalized patients receiving subcutaneous heparin 1.5 mg/kg TBW once daily or 1 mg/kg TBW twice daily. In both arms, the mean anti-Xa activity did not differ between normal-weight (BMI=18-30 kg/m^2) and overweight/obese (BMI>30 kg/m^2) individuals. In a study evaluating subcutaneous dalteparin in 10 patients with obesity and 10 matched non-obese patients indicated that mean volume of distribution in the group with obesity was not significantly greater than the control group, while clearance was. [13] It seems the evidence is somewhat confusing, although a nonlinear increase in drug clearance with increasing weight has been proposed. [4,14] In obesity, there is a risk of overdose of anticoagulants with weight-based dosing strategies and a risk of underdosing when prescribed in fixed doses. [1]

Clinical data

Obesity is a well-known risk factor for venous thromboembolism. [15] In the real world, however, patients with obesity are frequently undertreated, probably due to concerns regarding bleeding complications. In the CRUSADE registry data of over 19,000 patients with acute coronary syndrome, patients weighing >150 kg received a median weight-based enoxaparin dose of 0.65 mg/kg. Among those, patients who received the recommended weight-based dose (0.95–1.05 mg/kg), had an estimated excess bleeding risk of 2-fold that did not reach statistical significance (OR 2.42, 95% confidence interval 0.70-8.37). [16] This subgroup, the patients with BMI>40 or TBW>150 kg, are of particular interest. Actual body weight has been used to calculate the dose in patients weighing up to 160 kg in clinical trials for enoxaparin. [17] A retrospective study of 99 patients demonstrated that after the third dose of enoxaparin 1 mg/kg twice daily, 50% of patients had a supratherapeutic peak anti-Xa. [18] Furthermore, in another retrospective cohort study by Deal et al. in 26 patients with morbid obesity, the median starting dose of enoxaparin at 0.8 mg/kg of actual body weight (lower than the recommended regimen of 1 mg/kg), resulted in therapeutic or even higher anti- Xa levels at the majority of cohort patients (22 out of 26) [19] and in a cohort study of 31 patients with a BMI ≥40 kg/m^2 who were given 0.75 mg/kg twice daily, 48% had a therapeutic peak anti-Xa after the fourth dose, while 36% had a supratherapeutic level. [20]

Lee et al. analyzed 99 patients with BMI ≥40 kg/m^2 or TBW >150 kg who received enoxaparin in full dose (1mg/kg q12h or q24h if creatinine clearance (CrCl) was <30 mL/min). Fifty one percent (51%) had supratherapeutic levels, 35% had levels within the therapeutic range and 14% had subtherapeutic levels, while no bleeding complications were reported. [21] In a prospective cohort study, 41 patients mostly with morbid obesity (median weight of 138 kg and median BMI of 45.6 kg/m^2) and preserved renal function (GFR>30 mL/min) received therapeutic doses of enoxaparin. Although 15 patients weighed ≥150 kg, only one was prescribed a dose >150 mg. A logistic regression analysis revealed that dosing based on TBW was an independent predictor of a supratherapeutic anti-Xa level (OR = 0.21 and CI = 0.05-0.84 for <0.95-mg/kg dosing vs ≥0.95-mg/kg dosing). [22] Moreover, in a recently published retrospective study, the median therapeutic dose in patients with BMI of 40-50 kg/m^2, was 0.97 mg/kg every 12 h, in subjects with a BMI

of 50-60 kg/m^2, it was 0.70 mg/kg, and when BMI exceeded 60 kg/m^2 it was 0.71 mg/kg. [23]

The timing of drug administration has been under debate. The available evidence suggests that in patients with obesity, VTE recurs more often among those treated with enoxaparin once daily than twice daily, although this is not statistically significant. This difference in recurrence rates indicates that patients with obesity should not be treated with a once-daily dosing strategy of enoxaparin. The issue of the maximal anticoagulant dose also remains unclear. The need of capping the dose has not been yet established, but in most studies the enoxaparin dose did not exceed 150 mg twice daily, regardless of the body weight. In any case, probably because no trial has evaluated the use of adjusted body weight, total body weight (TBW) is mostly used to calculate anticoagulant dosing, but many authors recommend 0.7-0.8 mg/kg q12h subcutaneously if BMI ≥40 kg/m^2.[24,25]

Thromboembolic prophylaxis

There is evidence to support that less than 25 % of patients with morbid obesity receiving standard dosing of prophylactic anticoagulants (40 mg daily) achieve a desirable anti-Xa level (0.2-0.5 IU/mL). [26,27] Increased prophylactic dose to 0.5 mg/kg daily has been assessed in medical patients with morbid obesity in several trials. In patients with mean BMI=61 kg/m^2, 100% of patients achieved an anti-Xa level between 0.2 and 0.5 IU/mL on the second day of therapy versus only 25 % among those receiving standard doses of enoxaparin 40 mg daily. [28] The same dose in 28 patients with obesity (mean BMI 48.1 kg/m2) resulted in a mean peak anti-Xa level of 0.25 IU/mL. [29] In critically ill surgical patients, this dosing strategy achieved anti-Xa levels 0.2-0.5IU/ml in 86-91% of the individuals. [30,31]

In terms of clinical efficacy, enoxaparin 30 mg twice daily was compared to 40 mg twice daily in 481 patients with morbid obesity undergoing bariatric surgery (mean BMI 50.6 mg/m^2). The incidence of thrombosis was significantly lower among the higher dose recipients (5.4 % vs 0.6 %, p<0.01), with no increased risk for bleeding. [32] In a similar cohort, the 60 mg bid dose did not affect substantially the rate of thrombosis or bleeding compared to the 40 mg bid dose. [33] Finally, a retrospective study which included 9241 patients (3928 with morbid obesity), showed that patients with BMI >40 kg/m^2 who received higher prophylactic doses (enoxaparin 40 mg twice daily) exhibited a significant reduction in the rate of VTE as compared to those receiving standard dosing (enoxaparin 40 mg daily) (0.77 % vs. 1.48 %, p = 0.05). [34]

Recommendations regarding the optimal dosing scheme, prophylactic or therapeutic, are hard to elicit. Furthermore, the utility of measuring anti-Xa levels is controversial. Anticoagulant dose correlates with a predicable way with laboratory efficacy, and determining anti-X activity seems useful when other clinical conditions which can lead to over-anticoagulation coexist, apart from the obesity, such as renal dysfunction. Otherwise, its usefulness is not well established, since the trials evaluating anti-Xa levels did not reveal significant correlation with hemorrhagic or thrombotic events, both on preventive and therapeutic setting. [11,17,35-38] Thus, when prophylactic doses are used, anti-Xa monitoring does not seem necessary, while whenever the aim is treatment, each case should be assessed individually. [39] Given the more robust evidence provided by the trials with clinical outcomes and taking into account the opinion of the experts in the field, literature's propositions are summarized in the following Table 1.

Table 1. Summary of recommendations of enoxaparin use for prophylactic and therapeutic purposes [24,25].

	Prophylaxis	**Treatment**
BMI ≥40 kg/m^2	40 mg sc q12h	0.7-0.8 mg/kg TBW sc q12h Consider limiting each dose at 150 mg Avoid once-daily administration
BMI ≥50 kg/m^2	60 mg sc q12h	
Anti-Xa monitoring	Not particularly useful	Case specific individualization

BMI = body mass index; sc = subcutaneously; TBW = total body weight

Fondaparinux

Fondaparinux may be necessary in certain cases, when concerns about heparin-induced thrombocytopenia arise, for instance. Unfortunately, there is very minimal data regarding appropriate dosages of fondaparinux in patients with morbid obesity. One study of 45 patients with morbid obesity (mean BMI 51.2 kg/m2) showed that anti-Xa levels may be suboptimal in patients on a standard prophylactic dose of fondaparinux 2.5 mg daily, as anti-Xa levels were only within the institutional goal range 43 % of the time. [40] With regard to treatment dosing, subgroup analysis from the Matisse trial demonstrated no difference in terms of VTE recurrence at 3 months or major bleeding between individuals with BMI>30kg/m^2 or <30 kg/m^2. No

conclusive data exist, however, as the number of patients with a BMI >50 kg/m^2 was small and there is a theoretical risk of dose capping at 10 mg in this population. [41] Thus, no modification of the conventional dose can be supported in populations with morbid obesity.

In conclusion, the available evidence suggests that while standard fixed enoxaparin doses (for prophylactic purposes) carry a chance of unsatisfactory effect, the widely recommended weight-based dosing schemes may result in overtreatment, posing a risk of bleeding. Instead, a dose reduction in patients with morbid obesity will likely result in a therapeutic anti-Xa level without an increased probability for bleeding or VTE. Although TBW may not be the perfect parameter to base the dose calculations, due to the lack of data evaluating other metrics, all computations use TBW as the reference measure. Significant limitations of most of these data include the retrospective and observational design, and randomized controlled trials are needed in this patient population to conclusively determine the most appropriate enoxaparin dose.

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