

Original Article

Appropriate Enoxaparin Dose for Venous Thromboembolism Prophylaxis in Patients with Extreme Obesity

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ABSTRACT

Objective: To evaluate the appropriate dose of enoxaparin for venous thromboembolism (VTE) prophylaxis in patients with extreme obesity.

Methods: A literature search was performed using MEDLINE (1950-April 2013) to analyze all English-language articles that evaluated incidence of VTE and/or anti-Xa levels with enoxaparin for thromboprophylaxis in patients with extreme obesity.

Results: Eight studies were included in the analysis. Six of the studies were done in patients undergoing bariatric surgery. Mean body mass index ranged from 44.9 to 63.4 kg/m² within studies. Studies done with bariatric surgery patients utilized doses of enoxaparin that ranged from the standard dose of 30 mg subcutaneous (SQ) every 12 hours to 60 mg SQ every 12 hours. Other studies evaluated doses ranging from 40 mg SQ every 24 hours to 0.5 mg/kg/day. Only 3 studies evaluated the incidence of VTE as the primary endpoint; the other studies evaluated anti-Xa levels. The studies showed that appropriate anti-Xa levels were achieved more often with higher than standard doses of enoxaparin. One study showed that enoxaparin 40 mg SQ every 12 hours decreased the incidence of VTE in patients undergoing bariatric surgery compared to standard doses. Overall risk of bleeding was similar between study groups.

Conclusions: Higher than standard doses of enoxaparin may be needed for patients with extreme obesity. Patients undergoing bariatric surgery may benefit from enoxaparin 40 mg SQ every 12 hours. Additional large randomized, controlled trials are needed to determine the efficacy and safety of higher than standard doses of enoxaparin for VTE prophylaxis in patients with extreme obesity.

Key Words—enoxaparin, extreme obesity, prophylaxis venous thromboembolism

Hosp Pharm—2014;49:740–747

Prophylaxis of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and its extension pulmonary embolism (PE), is a mainstay of modern hospital care for many patients. In the United States, VTE is estimated to occur in up to 1 million people and accounts for over 200,000 deaths annually; more than half of VTE cases occur in the hospital setting.¹

When enoxaparin, one of the most commonly used low-molecular-weight heparins (LMWH), is chosen over viable alternatives for VTE prophylaxis, it is most often dosed at 40 mg subcutaneous (SQ) every 24 hours or 30 mg SQ every 12 hours.² For most patients, this has been proven to be a safe and effective dose.² However, these fixed doses do not take into consideration that the distribution of

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LMWH is weight based, and the efficacy of standard doses in obese and extreme obese patients may be decreased, putting these patients at a higher risk of thromboembolism.³⁻⁵

The Centers for Disease Control and Prevention (CDC) defines extreme obesity as a body mass index (BMI) of greater than or equal to 40.0 kg/m². With the CDC citing obesity and extreme obesity rates of 35.7% and 6.3% in the United States, an appropriate dosing strategy for enoxaparin thromboprophylaxis in these patients is needed.⁶

The most common laboratory test for monitoring the anticoagulation effect of enoxaparin is plasma anti-Xa level. This is an expensive test that is rarely performed due to the predictable pharmacodynamic profile of enoxaparin. Some patients may benefit from measuring anti-Xa levels. These include obese patients, patients with renal dysfunction, pediatric patients, and pregnant women. However, this recommendation is limited to patients receiving treatment doses of enoxaparin.² Measuring anti-Xa levels in patients receiving enoxaparin for thromboprophylaxis is not a proven predictor of outcomes, and there is no consensus about an appropriate therapeutic range. Sanofi-aventis reports that mean peak anti-factor Xa activity was found to be 0.16 IU/mL and 0.38 IU/mL after the 20 mg and 40 mg SQ doses, respectively, were clinically tested.⁷ It has been suggested in the literature that peak anti-Xa levels between 0.2 and 0.5 U/mL obtained 3 to 5 hours following SQ injections of enoxaparin will be appropriate for thromboprophylaxis.^{8,9}

Some studies have found a strong negative correlation between body weight and anti-Xa activity after a 40 mg SQ injection of enoxaparin.^{4,10} In addition, other studies have shown that obese and extremely obese patients may not achieve suggested anti-Xa levels when standard doses of enoxaparin are used for VTE prophylaxis.^{3,5,11}

The 2012 American College of Chest Physicians guidelines recommend the use of a LMWH such as enoxaparin or low-dose unfractionated heparin (LDUH) in 3 distinct categories of patient for VTE prophylaxis.² These include acutely ill patients with an increased risk of thrombosis and a low risk of bleeding, critically ill patients with a low risk of bleeding, and postsurgical patients with a moderate to high risk of VTE and a low risk of bleeding. The guidelines state, "It may be prudent to consult with a pharmacist regarding dosing in bariatric surgery patients and other patients who are obese who may require higher doses of LDUH or LMWH."^{2(pp270-271)}

Some institutions, including Temple University Hospital, are currently using higher than standard doses of enoxaparin for thromboprophylaxis in hospitalized patients with extreme obesity. Given the rise in the prevalence of extreme obesity, the purpose of this article is to provide an overview of the literature to better inform clinicians on the appropriate thromboprophylactic dose of enoxaparin in patients with extreme obesity.

LITERATURE REVIEW

There are no published multicenter, randomized, appropriately controlled, double-blinded clinical trials evaluating the dose of enoxaparin for VTE prophylaxis in patients with extreme obesity. Therefore we included small retrospective and prospective studies in this evaluation. Studies in the setting of bariatric surgery were included, because most patients undergoing bariatric surgery are extremely obese and require VTE prophylaxis. The endpoints of interest included incidence of VTE and anti-Xa levels. A total of 8 studies were evaluated. Only 3 studies evaluated incidence of VTE as their primary endpoint and only 2 studies evaluated the use of enoxaparin for thromboprophylaxis in extremely obese patients outside of the bariatric surgery setting. Table 1 presents a summary of the studies included.

Studies That Evaluated Anti-Xa Levels in Bariatric Surgery Patients

In 2007, Rowan et al compared 2 different dosing regimens of enoxaparin for VTE prophylaxis in 52 hospitalized patients undergoing laparoscopic banding or laparoscopic gastric bypass surgery.¹² Patients received either enoxaparin 30 mg SQ every 12 hours or 40 mg SQ every 12 hours. The primary endpoint of the study was percent of patients achieving appropriate anti-Xa levels (defined as a level between 0.18 and 0.4 U/mL) 4 hours after the first and third doses of enoxaparin. After the first dose, 30.8% of the patients receiving 40 mg were within an appropriate therapeutic range compared to 0% in the group receiving 30 mg ($P = .01$). After the third dose, only 41% of patients in the 40 mg group and 9% of patients in the 30 mg group were within therapeutic range ($P = .115$). No bleeding events were reported. The results of this study imply that 30 mg every 12 hours may not be enough to achieve the desired anti-Xa levels and that 40 mg every 12 hours shows only a slight improvement over the 30 mg regimen.

Table 1. Summary of studies

Study	Study design	Population	Outcomes	Intervention	Selected baseline characteristics	Efficacy results	Safety results
Rowan et al, 2007 ¹²	Single center, prospective, nonrandomized	Bariatric surgery patients	Primary: Percent of patients with anti-Xa levels between 0.18 and 0.44 U/mL	30 mg SQ every 12 hours	N = 19 74% female Mean BMI: 48.4 ± 7.1 Mean age: 41.7 years Mean score: 1.0	0% after 1st dose; 9.1% after 3rd dose	N/A
				40 mg SQ every 12 hours	N = 33 82% female Mean BMI: 48.5 ± 8.5 Mean age = 40.8 years Mean score = 0.9	30.8% after 1st dose; 41.7% after 3rd dose	N/A
Simone et al, 2008 ¹³	Single center, prospective, nonrandomized	Bariatric surgery patients	Primary: Mean anti-Xa levels measured 4 hours after 1st and 3rd dose	40 mg SQ every 12 hours	N = 22 87.5% female Mean BMI: 48.8 ± 6.6 Mean age: 40.0 years Mean score: 1.0	Mean anti-Xa level: 0.17 U/mL after 1st dose; 0.21 U/mL after 2nd dose	1 major bleeding event (6.3%)
				60 mg SQ every 12 hours	N = 16 93.7% female Mean BMI: 47.3 ± 6.6 Mean age: 41.0 years Mean score: 0.9	Mean anti-Xa level: 0.26 U/mL after 1st dose; 0.43 U/mL after 2nd dose	0 major bleeding events
Borkgren-Okonek et al, 2008 ¹⁴	Single center, prospective, nonrandomized	Bariatric surgery patients	Primary: Percent of patients with anti-Xa levels between 0.18 and 0.44 U/mL measured 4 hours after 3rd dose Secondary: VTE and major bleeding	40 mg SQ every 12 hours (BMI < 50 kg/m ²)	N = 124 77% female Mean BMI: 44.9 (36-50) Mean age: 44.7 years	79% in therapeutic range; 21% subtherapeutic; 0% supratherapeutic 1 VTE post operative day 37	4 major bleeding events
				60 mg SQ every 12 hours (BMI > 50 kg/m ²)	N = 99 73% female Mean BMI: 57.4 (51-82) Mean age: 44.3 years	69% within therapeutic range; 14% subtherapeutic; 17% supratherapeutic	1 major bleeding event
Scholten et al, 2002 ¹⁸	Single center, prospective, nonrandomized	Bariatric surgery patients	Primary: Incidence of VTE Secondary: Major bleeding	30 mg SQ every 12 hours	N = 92 79.8% female Mean BMI: 51.7	5 VTE events (5.4 %)	1 major bleeding event
				40 mg SQ every 12 hours	N = 389 84.2% female Mean BMI: 50.3	2 VTE events (0.6 %)	1 major bleeding event

(continued)

Table 1. Summary of studies (CONT.)

Study	Study design	Population	Outcomes	Intervention	Selected baseline characteristics	Efficacy results	Safety results
Hamad, & Chohan, 2005 ¹⁹	Multicenter, retrospective, nonrandomized	Bariatric surgery patients	Primary: Incidence of VTE Secondary: Major bleeding	Variable by center – from 30 mg SQ every 24 hours to 40 mg SQ every 12 hours	N = 668 86% female Mean BMI: 49.6 ± 8.4 Mean age: 39-47 years	7 VTE events (1.05%)	6 major bleeding events (0.9%)
Escalante-Tattersfield et al, 2008 ²⁰	Single center, prospective, nonrandomized	Bariatric surgery patients	Primary: Incidence of DVT Secondary: Major bleeding	40 mg SQ every 12 hours	N = 451 73% female Mean BMI: 49 (35-90) Mean age: 44 years	1 VTE, asymptomatic (0.22%)	No major bleeding
Ludwig et al, 2011 ²³	Single center, retrospective	SICU patients	Primary: Percent of patients with anti-Xa levels between 0.2 and 0.5 U/mL 4 to 6 hours after 3rd or 4th dose	0.5 mg/kg SQ every 12 hours until SICU discharge	N = 23 57% female Mean BMI: 46.4 (36-77) Mean age: 45.6 years	91% within therapeutic range; 9% supratherapeutic 1 DVT (4.3%)	No major bleeding events
Freeman et al, 2012 ²⁴	Single center, prospective	Hospitalized medically ill patients	Primary: Percent anti-Xa levels (0.2-0.5 U/mL) 4 to 6 hours after dose Secondary: VTE, bleeding	40 mg SQ once daily	N = 11 81.8% female Mean BMI: 63.4 ± 11.6 Mean age: 45.5 years Mean CrCl: 84	18% within therapeutic range; 82% subtherapeutic No VTEs	No bleeding events
				0.4 mg/kg/day	N = 9 33.3% female Mean BMI: 60.7 ± 12.4 Mean age: 43.8 years Mean CrCl: 135	53% within therapeutic range; 36% subtherapeutic; 11% supratherapeutic No VTEs	No bleeding events
				0.5 mg/kg/day	N = 11 72.7% female Mean BMI: 61.3 ± 12.2 Mean age: 42.7 years Mean CrCl: 139	87% within therapeutic range; 13% subtherapeutic No VTEs	No bleeding events

Note: BMI = body mass index (kg/m²); CrCl = creatinine clearance (mL/min); DVT = deep vein thrombosis; SCr = serum creatinine; SICU = surgical intensive care unit; SQ = subcutaneous; VTE = venous thromboembolism.

In 2008, Simone et al built on the Rowan study by performing a similar analysis using 40 mg or 60 mg SQ every 12 hours.¹³ These patients were also undergoing laparoscopic banding or laparoscopic gastric bypass surgery. The primary endpoint of the study was mean anti-Xa levels. After the first dose of enoxaparin, the mean anti-Xa levels were 0.17 U/mL in the 40 mg group and 0.26 U/mL in the 60 mg group ($P < .005$), placing the 40 mg group below the appropriate therapeutic range (defined as a level between 0.18 and 0.44 U/mL). After the third dose, mean anti-Xa levels were 0.21 U/mL in the 40 mg group and 0.43 U/mL in the 60 mg group ($P < .001$). The study showed that after the third dose, even though mean anti-Xa levels were higher in the 60 mg group, both groups achieved a therapeutic anti-Xa level. There was one major bleeding event in the 40 mg group.

Borkgren-Okonek et al evaluated a different approach and divided a population of bariatric surgery patients into those with BMI less than or equal to 50 kg/m² and those with BMI greater than 50 kg/m².¹⁴ Patients with a BMI less than or equal to 50 kg/m² were given 40 mg of enoxaparin SQ every 12 hours, while patients with BMI greater than 50 kg/m² were given 60 mg SQ every 12 hours. The primary endpoint was the percentage of patients with anti-Xa levels between 0.18 and 0.44 U/mL measured 4 hours after the third dose. More than 90% of patients in this study underwent laparoscopic gastric bypass surgery. A total of 79% of patients in the 40 mg group and 69% of patients in the 60 mg group were able to achieve a desired anti-Xa level. In the 40 mg group, none of the patients were suprathreshold, whereas the 60 mg group showed similar numbers of patients with subtherapeutic and suprathreshold levels. There were 5 major bleeding events, 4 of them in the 40 mg group. This study showed that higher than standard doses of enoxaparin are effective in patients with extreme obesity; the higher the BMI, the higher the dose needed to achieve appropriate anti-Xa levels.

The results of the previous 3 studies need to be assessed with caution primarily due to the controversy about the appropriate anti-Xa levels for thromboprophylaxis and the large variability in reported anti-Xa levels between different laboratories. The methods to perform anti-Xa assays are usually not standardized.¹⁵ Nevertheless, all the investigators tried to strengthen the design of the studies by evaluating anti-Xa levels 4 hours after the third dose, making sure the levels are at steady state.¹⁶

When analyzing the results of these studies, it is also important to take into consideration that most of the patients in the studies had good renal function. The mean serum creatinine (SCr) of the patients in the first 2 studies was normal, and most patients were in their early forties. The study by Borkgren-Okonek excluded patients with SCr greater than 1.6 mg/dL. Therefore it is not clear if their results can be extrapolated to patients with renal dysfunction. Enoxaparin accumulates in renal dysfunction¹⁷ and the anti-Xa levels may be higher if the dose is not adjusted, putting the patients at a higher risk of bleeding.

Of the 3 studies, Borkgren-Okonek et al had the strongest design. It was the largest of the 3 studies, with 223 patients, and the only study that evaluated incidence of VTE and bleeding (as secondary endpoints). This is probably the reason why the number of patients with major bleeding was higher in this study than in the others. However, this study was not powered to assess the relationship between anti-Xa levels and risk of VTE and/or bleeding.

Studies That Evaluated Incidence of VTE in Bariatric Surgery Patients

In 2002, Scholten et al compared the use of enoxaparin 30 mg SQ every 12 to enoxaparin 40 mg SQ every 12 hours in 481 patients undergoing bariatric surgery.¹⁸ Enoxaparin was given 2 hours prior to surgery and continued until the patients were fully ambulatory or until hospital discharge. Most patients (97.5%) underwent open long limb Roux-en-Y gastric bypass surgery. In this study, the incidence of VTE was higher in the group receiving 30 mg SQ every 12 hours (5/92 [5.6%] vs 2/389 [0.6%]; $P < .01$). Two of the episodes occurred during hospital stays in the group receiving 30 mg SQ every 12 hours. Major bleeding was similar between groups (one event in each group). Even though this was a relatively large study, the authors agree that the results could have been skewed because patients in the group of 30 mg SQ every 12 hours had a longer duration of hospital stay (5.6 days vs 3.8 days; $P < .05$) and a longer procedure time (213 min vs 175 min; $P < .05$) than patients in 40 mg SQ every 12 hours.

In 2005, the prophylaxis against VTE outcomes in bariatric surgery patients receiving enoxaparin study (PROBE) investigators performed a retrospective analysis of enoxaparin prophylaxis dosing in bariatric surgery patients at 5 medical centers.¹⁹ The perioperative dosing regimen of enoxaparin varied among the 5 medical centers, ranging from 30 to 40 mg SQ every 24 to 12 hours. Only one

center used a dose of 40 mg SQ every 12 hours. The duration of enoxaparin varied between centers from 12 hours to 10 days. Most patients (85%) underwent open surgical procedures, either gastric bypass or vertical banded gastroplasty. There were 6 PEs and 1 DVT recorded; 6 of the 7 episodes occurred after discontinuation of enoxaparin. The patient who developed a PE while on enoxaparin was receiving 30 mg every 24 hours. The highest rate of VTE was found in the center that provided a dose of 30 mg every 24 hours post discharge (with 3 of the 7 episodes). The study did not evaluate differences in patients' demographics or the risk of VTE with the different dosing regimens. The authors concluded that the doses used for VTE prophylaxis were adequate, but extending the duration of enoxaparin may be of value.

Escalante-Tattersfield et al evaluated the use of 40 mg of enoxaparin SQ every 12 hours after surgery and continued for 10 days after discharged in 451 bariatric surgery patients.²⁰ All patients underwent laparoscopic gastric bypass surgery. The primary endpoint in this study was incidence of DVT. In this study, only 1 case of asymptomatic DVT (0.22%) was discovered by ultrasound on postoperative day 1. There were no major bleeding events requiring discontinuation of enoxaparin. Even though this study had a good amount of patients, it did not compare different dosing strategies. The authors concluded that the low rate of DVT was probably due to the use of enoxaparin.

In the Borkgren-Okonek et al study, patients were given 40 mg of enoxaparin SQ every 12 hours if their BMI was less than or equal to 50 kg/m² or 60 mg SQ every 12 hours if their BMI was greater than 50 kg/m².¹⁴ Enoxaparin was started 12 hours after surgery and was continued for 10 days after discharge. The incidence of VTE was a secondary endpoint of this study. Only 1 patient had a confirmed DVT after enoxaparin was discontinued (this patient was receiving 40 mg SQ every 12 hours). Five patients (2.24%) in this study had major bleeds while receiving enoxaparin, requiring either transfusion or reoperation. It was not clear, however, that these bleeds were all related to enoxaparin therapy. Four of the 5 bleeding events occurred in the lower dose group. The authors concluded that using higher than standard dosing and stratifying patients by BMI was effective at preventing VTEs.

All the studies that evaluated incidence of VTE in patients with extreme obesity are limited by their design. None of the studies were randomized or

double-blinded, only one study was multicenter, and most of the studies did not control for confounders. This can create selection bias when the results are evaluated and decreases applicability. The single center design of these studies decreases their applicability, because there is considerable variability in the approach of preventing VTE among bariatric surgery programs.²¹ For example, some of these trials mentioned the placement of inferior vena caval filters prior to bariatric surgery in patients at high risk of thromboembolism. However, the strength of the studies included the use of appropriate techniques to evaluate VTEs (they all used Doppler ultrasound, V/Q scan, and/or CT scan).

Because all of the studies involved patients undergoing bariatric surgery, the incidence of VTE in these trials may not represent the incidence of VTE in other patient populations. It is also important to keep in mind that most of the studies utilized combination thromboprophylaxis (compression devices and early ambulation), which will decrease the incidence of VTE. On the other hand, most of the patients in the trials had 2 or more risk factors for VTE (including major surgery), making their incidence of VTE higher than that in populations of extremely obese patients without additional risk factors.²² Finally, the results of these studies could underestimate the risk of VTE, because only one of the studies looked for asymptomatic VTE.²⁰

Major bleeding was defined similarly in all studies (significant decrease in hemoglobin >2 g/dL, transfusion, and/or reoperation), and its incidence was considered small. However, none of these studies mentioned the inclusion of patients with renal dysfunction. Most of the patients in these studies were in their early forties, and we can assume that most patients did not have renal insufficiency. Of the 4 studies, only 1 excluded patients with SCr greater than 1.6 mg/dL (Borkgren-Okonek et al). As mentioned before, this could have minimized the risk of bleeding in this patient population.¹⁷

Finally, it is important to recognize that the Scholten and Hamad studies had the highest incidence of VTE events, with 7 VTEs in each study. These studies were done in the early 2000s, and in both studies most patients underwent open surgical procedures instead of laparoscopic procedures, which is now the type of procedure most commonly done. The duration of hospital stay was also longer in these studies, ranging from 2 to 6 days, and enoxaparin was stopped earlier than in the other studies (12 hours to 5 days after surgery). The study by Scholten had

the highest duration of hospital stay. All of these factors could have accounted for the higher incidence of VTEs compared to the studies done by Escalante-Tattersfield and Borkgren-Okonek. Also, the studies with a lower incidence of VTE used higher than standard doses of enoxaparin and continued enoxaparin for 10 days after discharge. This may be the appropriate duration of therapy to prevent VTEs in this patient population.

Studies That Evaluate Anti-Xa Levels in Medically/Surgically Ill Patients

In 2011, Ludwig et al conducted a retrospective study in patients with BMI greater than 35 kg/m² or weight greater than 150 kg in a surgical intensive care unit.²³ Different from the studies done in bariatric surgery patients, this study evaluated a weight-based enoxaparin regimen (0.5 mg/kg every 12 hours). The primary endpoint was percent of patients with therapeutic anti-Xa levels (0.2 to 0.5 U/mL) 4 hours after the third or fourth dose. The results of this study showed that 91% of patients were in therapeutic range and the remaining 9% were supratherapeutic. The study also showed 1 DVT (4.3%) and no major bleeding events.

In 2012, Freeman et al evaluated the use of different thromboprophylactic doses of enoxaparin in 31 hospitalized, medically ill patients.²⁴ Extremely obese patients received either fixed dose (FD) enoxaparin 40 mg SQ daily, lower dose (LD) enoxaparin 0.4 mg/kg/day SQ daily, or higher dose (HD) enoxaparin 0.5 mg/kg/day SQ daily. The primary endpoint was percent of patients achieving anti-Xa level between 0.2 and 0.5 U/mL. This was measured daily 4 to 6 hours after the dose while the patients were hospitalized. The results showed that more patients (more than 80%) in the HD group achieved the targeted anti-Xa levels when compared to the other groups ($P < .001$). No bleeding or thrombotic events were reported in any of the 3 groups.

These results are promising and offer a novel dosing strategy for extremely obese patients outside the bariatric surgery setting, but the studies are limited by their small sample size and the pharmacodynamics outcome measured. It is important to note that the appropriate anti-Xa range was slightly different between these studies and the studies done in bariatric surgery patients (0.18-0.44 U/mL vs 0.2-0.5 U/mL). The significance of this is not known. However, these 2 small studies provide evidence that higher than standard doses of enoxaparin in patients

with extreme obesity may also be needed outside the bariatric surgical setting.

SUMMARY

There is evidence that standard doses of enoxaparin for VTE prophylaxis may not provide optimal protection to patients with extreme obesity. The use of higher than standard doses in these patients will make sense, because the dose of enoxaparin for treatment of VTE is based on patients' weight. However, at the moment, the most appropriate dose of enoxaparin for VTE prophylaxis in patients with extreme obesity is still not clear. The studies that have tried to answer this question using higher than standard dosing fall short of providing an answer that can be applied with confidence in clinical practice, especially outside the bariatric surgical setting. Most of the studies are done in patients undergoing bariatric surgery, and these patients are known to have higher bleeding risks and higher BMIs and may have more risk factors for VTE than other patients with extreme obesity.

In the bariatric surgical patient, the strongest data seem to support the use of 40 mg of enoxaparin SQ every 12 hours. The use of this dose was shown to decrease the risk of VTE in patients undergoing bariatric surgery and to bring more patients to a desired anti-Xa level when compared to standard doses.

In the nonbariatric surgical setting, there are limited data; only 2 studies have been published. One of the studies is in surgical intensive care unit (ICU) patients and the other in non-ICU medically ill patients. Both studies used a dose of 0.5 mg/kg/day that was shown to be effective and safe in these patients. However, the studies only included a small number of patients.

Pharmacists need to individualize the dose of enoxaparin for patients with BMI greater than 40 kg/m² based on the patients' risk of bleeding and thromboembolism. If the risk of bleeding is not high, doses of 40 mg SQ every 12 hours seem to be a safe and effective strategy.

Additional large, randomized, controlled trials that evaluate the incidence of VTE in patients with extreme obesity, in different hospital settings, are needed to determine the efficacy and safety of higher than standard doses of enoxaparin for VTE prophylaxis.

ACKNOWLEDGMENTS

The authors declare no conflicts of interest.

REFERENCES

1. *The Surgeon General's Call to Action to Prevent Deep Vein Thrombosis and Pulmonary Embolism*. Washington, DC: US Department of Health and Human Services; 2008.
2. Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in non-orthopedic surgical patients. Antithrombotic therapy and prevention of thrombosis, 9th ed. American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2 Suppl):e227S-77S.
3. Rodina MT, Wheeler M, Rodgers GM, Draper L, Pendleton RC. Weight-based dosing of enoxaparin for VTE prophylaxis in morbidly obese, medically-ill patients. *Thromb Res*. 2010;125:220-223.
4. Frederiksen SG, Hedenbro JL, Norgren L. Enoxaparin effect depends on body-weight and current doses may be inadequate in obese patients. *Br J Surg*. 2003;90:547-548.
5. Sanderink GJ, Le Liboux A, Jariwala N, et al. The pharmacokinetics and pharmacodynamics of enoxaparin in obese volunteers. *Clin Pharmacol Ther*. 2002;72(3):308-318.
6. Centers for Disease Control and Prevention. Obesity and overweight for professionals: Adult - DNPAO - CDC. April 27, 2012. <http://www.cdc.gov/obesity/adult/index.html>. Accessed June 19, 2012.
7. Enoxaparin sodium [package insert]. Bridgewater, NJ: Sanofi-aventis U.S. LLC; 2013.
8. Lim W. Using low molecular weight heparin in special patient populations. *J Thromb Thrombolysis*. 2010;29:233-240.
9. Nutescu EA, Spinler SA, Wittkowsky A, Dager WE. Low-molecular-weight heparins in renal impairment and obesity: Available evidence and clinical practice recommendations across medical and surgical settings. *Ann Pharmacother*. 2009;43(6):1064-1083.
10. Mayr AJ, Dunser M, Jochberger S, et al. Antifactor Xa activity in intensive care patients receiving thromboembolic prophylaxis with standard doses of enoxaparin. *Thromb Res*. 2002;105:201-204.
11. Rondina MT, Wheeler M, Rodgers GM, et al. Effect of obesity on outcomes after fondaparinux, enoxaparin, or heparin treatment for acute venous thromboembolism in the Mattisse trials. *J Thromb Haemostasis*. 2007;5:1191-1194.
12. Rowan B, Kuhl D, Lee M, et al. Anti-Xa levels in bariatric surgery patients receiving prophylactic enoxaparin. *Obes Surg*. 2008;18:162-166.
13. Simone EP, Madan AK, Tichansky DS, Kuhl DA, Lee MD. Comparison of two low-molecularweight heparin dosing regimens for patients undergoing laparoscopic bariatric surgery. *Surg Endosc*. 2008;22:2392-2395.
14. Borkgren-Okonek M, Hart R, Pantano J, et al. Enoxaparin thromboprophylaxis in gastric bypass patients: Extended duration, dose stratification, and antifactor Xa activity. *Surg Obes Relat Dis*. 2008;4:625-631.
15. Favaloro EJ, Bonar R, Aboud M, et al. How useful is the monitoring of (low molecular weight) heparin therapy by anti-Xa assay? A laboratory perspective. *Lab Hematol*. 2005;11:157-162.
16. Laposata M, Green D, Van Cott EM, Barrowcliffe TW, Goodnight SH, Sosolik RC. College of American Pathologists Conference XXXI on laboratory monitoring for low molecular weight heparin, danaparoid, hirudin and related compounds, and argatroban. *Arch Pathol Lab Med*. 1998;122:799-807.
17. Sanderink GJ, Guimart CG, Ozoux ML, Jariwala NU, Shukla UA, Boutouyrie BX. Pharmacokinetics and pharmacodynamics of the prophylactic dose of enoxaparin once daily over 4 days in patients with renal impairment. *Thromb Res*. 2002;105(3):225-231.
18. Scholten DJ, Hoedema RM, Scholten SE. A comparison of two different prophylactic dose regimens of low molecular weight heparin in bariatric surgery. *Obes Surg*. 2002;12(1):19-24.
19. Hamad GG, Choban PS. Enoxaparin for thromboprophylaxis in morbidly obese patients undergoing bariatric surgery: Findings of the prophylaxis against VTE outcomes in bariatric surgery patients receiving enoxaparin (PROBE) study. *Obes Surg*. 2005;15(10):1368-1374.
20. Escalante-Tattersfield T, Tucker O, Fajnwaks P, et al. Incidence of deep vein thrombosis in morbidly obese patients undergoing laparoscopic Roux-en-Y gastric bypass. *Surg Obes Relat Dis*. 2008;4:126-130.
21. Wu EC, Barba CA. Current practices in the prophylaxis of venous thromboembolism in bariatric surgery. *Obes Surg*. 2000;10:7-13.
22. Holmes NJ, Brodin RE, Kaufman JL. Is morbid obesity a risk factor for postoperative venous thromboembolism? *Infect Med*. 1994;11:273-278.
23. Ludwig KP, Simons HJ, Mone M, Barton RG, Kimball EJ. Implementation of an enoxaparin protocol for venous thromboembolism prophylaxis in obese surgical intensive care unit patients. *Ann Pharmacother*. 2011;45:1356-1362.
24. Freeman A, Horner T, Pendleton RC, et al. Prospective comparison of three enoxaparin dosing regimens to achieve target anti-factor Xa levels in hospitalized, medically ill patients with extreme obesity. *Am J Hematol*. 2012;87(7):740-743. ■