



Utilization of Low Molecular Weight Heparins in Special Populations: Renal Impairment and Obesity

Angela Shogbon, PharmD, BCPS and Janene Marshall, PharmD, Last updated: June 2011

This clinical pearl focuses on the utilization of dalteparin and enoxaparin in patients with renal impairment and obesity. These agents are indicated for thromboprophylaxis in various patient populations, for treatment of venous thromboembolism (VTE), and in the management of acute coronary syndrome (ACS). In this review, severe renal insufficiency is defined as creatinine clearance (CrCl) < 30 ml/min and morbid obesity is defined as a weight greater than 190kg or BMI greater than or equal to 40kg/m².

Renal Impairment

- 1.) What are current concerns with use of LMWHs in severe renal impairment?
 - The greater renal clearance of LMWH leads to concerns with drug accumulation in renal impairment¹
 - Patients with severe renal insufficiency receiving treatment dose LMWH could be prone to adverse events from needlessly excessive doses and accumulation of the drug
 - Enoxaparin has a greater renal clearance compared with dalteparin and has been better studied in renal impairment
 - LMWHs are not fully reversible compared to unfractionated heparin¹
- 2.) What is the recommended monitoring of LMWH in severe renal impairment?
 - Anti-factor Xa levels utilized as a surrogate biomarker of LMWHs anticoagulant effect²
 - Anti-factor Xa levels do not need to be routinely monitored in most patients on LMWHs³
 - In patients with severe renal impairment (CrCl < 30 ml/min), anti-factor Xa level monitoring is recommended due to uncertainty with the appropriate dosing and safety of LMWH in this population³
 - Peak anti-factor Xa levels are obtained about 4 hours after the dose of the LMWH and after about 3 – 4 doses of the LMWH have been received
- 3.) What are the dosing recommendations of dalteparin and enoxaparin in patients with severe renal insufficiency?

Dalteparin⁴ - No dose adjustment recommended with severe renal impairment (CrCl < 30 ml/min) and initial dosing based on indication:

- Prophylaxis: Dalteparin 2500-5000 int. units SC once daily
 - No significant risk for drug accumulation expected with prophylactic doses with short term use (< 10 days);^{5,6} if longer therapy needed, consider monitoring anti-factor Xa levels and adjust dose if accumulating⁷
- Treatment: Dalteparin 100-120 int. units/kg SC Q12H
 - Recommended to monitor anti-factor Xa levels with adjustment of dose as necessary based on levels obtained; no set guidelines available on how to adjust doses based on obtained anti-factor Xa levels

Enoxaparin⁸ - Dose adjusted based on CrCl and initial dosing based on indication

- Prophylaxis: CrCl ≥ 30 ml/min - Enoxaparin 30 mg SC Q12H OR Enoxaparin 40 mg SC daily
CrCl < 30 ml/min - Enoxaparin 30 mg SC once daily
- Treatment: CrCl ≥ 30 ml/min - Enoxaparin 1 mg/kg SC Q12H
CrCl < 30 ml/min - Enoxaparin 1 mg/kg SC once daily

- Consider monitoring of anti-Xa levels with extended use (> 10 days) of enoxaparin in patients with moderate renal impairment (30-60 ml/min) to assess for possible drug accumulation
 - Not FDA approved for use in dialysis patients, consider alternative anticoagulant as accumulation expected
- 4.) How should pharmacists approach the use of LMWHs in patients with severe renal impairment?
- Evaluate renal function and its stability; calculate CrCl utilizing the Cockcroft-Gault equation^{7,9}
 - In patients with severe renal insufficiency who require therapeutic anticoagulation, the American College of Chest Physicians suggests the use of UFH instead of LMWH³
 - If LMWH chosen, utilize manufacturer recommended dosage adjustment for enoxaparin for patients not on hemodialysis
 - Consider use of twice daily dosing regimen for dalteparin to prevent high peak anti-Xa levels⁹
 - Anti-factor Xa levels should be monitored and dose adjusted accordingly to maintain lab defined therapeutic range⁹
 - Avoid use of LMWH in severe renal insufficiency if anti-Xa levels cannot be monitored⁹
 - Monitor patients carefully for signs and symptoms of bleeding

Obesity

- 1.) What are current concerns with use of LMWHs in obesity?
- Standard recommended doses may not be enough to prevent VTE in obese patients^{7,10}
 - Capping doses of LMWH may be unsafe due to the risk of under-dosing in the obese patient¹⁰
 - Use of higher doses may lead to increased risk of bleeding¹⁰
 - There is uncertainty of when to obtain anti-factor Xa levels for monitoring¹¹
- 2.) What is the recommended monitoring of LMWH in obese patients⁷
- Anti-factor Xa levels should be considered for patients who are morbidly obese (i.e., weigh greater than 190 kg or have BMI greater than 40 kg/m²)
 - Peak anti-factor Xa levels should be drawn 4 hours following subcutaneous injections
 - Each laboratory should provide LMWH specific therapeutic ranges for anti-factor Xa levels
 - A specific method for adjustment of doses based upon obtained anti-Xa levels has not been recommended
- 3.) What are the dosing recommendations of dalteparin and enoxaparin in patients with obesity?
- The 8th edition of the CHEST guidelines recommends weight based dosing for both prophylaxis and treatment of an acute deep vein thrombosis (DVT)

Dalteparin:

- Prophylaxis:¹² Dalteparin 7500 int. units q 24h.
 - This recommendation is based on clinical studies since the current FDA approved dosing provides no specific dose adjustment in obese patients
- Treatment: Dalteparin 200 – 240 int. units/kg/day⁴
 - The manufacturer reports not to exceed 18,000 int. units/day for DVT/PE treatment and 10,000 int. units SC every 12 hours for ACS treatment, however, literature has shown that most patients still reach target anti-factor Xa range without dose capping at a ceiling dose¹²

Enoxaparin:

- Prophylaxis: Clinical literature has recommended doses of Enoxaparin ranging from 0.5mg/kg SC Q12h or a 25% increase from the standard prophylaxis dose¹¹
- Bariatric Surgery (Roux-en-Y gastric bypass):^{13,14}
BMI ≤50 kg/m²: 40 mg every 12 hours

BMI >50 kg/m²: 60 mg every 12 hours

- Treatment:^{7,11,15} Dose should be based on actual body weight 1mg/kg SC Q12H for the inpatient (or 1.5mg/kg SC Q24H for outpatient) is sufficient to reach appropriate levels in the body
 - Consider monitoring anti-Xa levels in patients weighing ≥ 190 kg

4.) How should pharmacists approach the use of LMWHs in obese patients?

- Consider increasing recommend prophylaxis dose of enoxaparin by 25% or increasing the dose to 0.5mg/kg q 12h in obese patients, for dalteparin consider increasing the dose to 7500 IU/day
- When treating an obese patient for VTE or ACS, capping doses has not been shown to be safer than dosing by body weight and patients have still been found to reach therapeutic anti-Xa levels
- If bleeding is a concern, use UFH instead of LMWH

References

1. Lim W, Dentali F, Eikeelboom JW, and Crowther MA. Meta-analysis: low-molecular-weight heparin and bleeding in patients with severe renal insufficiency. *Ann Intern Med* 2006;144:673-684
2. Symes J. Low molecular weight heparins in patients with renal insufficiency. *CANNT J* 2008;18(2):55-61
3. Hirsh J, Bauer KA, Donati MB et al. Parenteral anticoagulants: American college of Chest Physicians evidence-based clinical practice guidelines (8th edition). *CHEST* 2008;133:141S-159S
4. Pfizer Inc. Fragmin (dalteparin) package insert. New York, NY; 2007.
5. Tincani E, Mannucci C, Casolari B, et al. Safety of dalteparin for the prophylaxis of venous thromboembolism in elderly medical patients with renal insufficiency: a pilot study. *Haematologica* 2006; 91:976-979
6. Cook D, Douketis J, Meade M, et al. Venous thromboembolism and bleeding in critically ill patients with severe renal insufficiency receiving dalteparin thromboprophylaxis: prevalence, incidence and risk factors. *Crit Care*. 2008; 12(2): R32
7. Nutescu EA, Spinler SA, Wittkowsky A, Dager W. Low-molecular-weight heparins in renal impairment and obesity: available evidence and clinical practice recommendations across medical and surgical settings. *Ann Pharmacother* 2009;43:1064-83.
8. Sanofi-aventis. Lovenox (enoxaparin) package insert. Bridgewater, NJ; 2009
9. Schmid P, Fischer AG, Wuillemin WA. Low-molecular-weight heparin in patients with renal insufficiency. *Swiss Med Wkly* 2009;139:438-452
10. LMWH dosing in obesity. *Pharmacist's Letter/Prescriber's Letter*. 2008;24(2):240212.
11. Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of Venous Thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest June 2008 133:381S-453S*.
12. Smith J, Canton EM. Weight-Based Administration of Dalteparin in Obese Patients. *AJHP*. 2003;60(7):683-686
13. Borkgren-Okonek MJ, Hart RW, Pantano JE, et al, "Enoxaparin Thromboprophylaxis in Gastric Bypass Patients: Extended Duration, Dose Stratification, and Antifactor Xa Activity," *Surg Obes Relat Dis*, 2008, 4(5):625-31.
14. 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.
15. Duplaga BA, Rivers CW, Nutescu E. Dosing and monitoring of low-molecular-weight heparins in special populations. *Pharmacotherapy* 2001;21:218-34

Other relevant references

- Egger SS, Sawatzki MG, Drewe J and Krahenbuhl S. Life-threatening hemorrhage after dalteparin therapy in a patient with impaired renal function. *Pharmacotherapy* 2005;25(6):881-885
- Schmid P, Brodmann D, Odermatt Y, Fischer AG, Wuillemin WA. Study of bioaccumulation of dalteparin at a therapeutic dose in patients with renal insufficiency. *J Thromb Haemost* 2009;7:1629-32
- Simoneau MD, Vachon A, Picard F. Effect of prophylactic dalteparin on anti-factor Xa levels in morbidly obese patients after bariatric surgery. *Obes Surg*. 2008 Oct 18. [Epub ahead of print]
- Simone EP, Madan AK, Tichansky DS, Kuhl DA, Lee MD. Comparison of two low-molecular-weight heparin dosing regimens for patients undergoing laparoscopic bariatric surgery. *Surg Endosc*. 2008;22(11):2392-2395.
- Hamad GG, Chohan PS. Enoxaparin for the 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.
- [Bazinet A, Almanic K, Brunet C](#), et al. Dosage of enoxaparin among obese and renal impairment patients. [Thromb Res](#). 2005;116(1):41-50. Epub 2004 Nov 6.

Disclaimer:

This resource was developed by those members of the ASHP New Practitioners Forum identified herein, who are providing other members the opportunity to share resources that might assist in professional endeavors. ASHP is not responsible for, and does not officially endorse this resource, and further expressly disclaims any and all liability for damages of any kind arising out of the use, reference to, or reliance upon any information contained in the resource. No guarantee is provided that the content is correct, accurate, complete, up-to-date or owned by the individual who posted it. ASHP has not participated in the development of the content, and does not exert any editorial control over it. All content consists solely of material supplied from contributors, and the opinions and statements expressed by contributors are solely those of the individual writers, and do not reflect the opinions of ASHP or its officers, directors or employees. The names and contact information contained in this resource are published to facilitate communication, and such information shall not be used for commercial purposes. Reference to any specific commercial entity, product, service or process does not constitute endorsement, recommendation, favoring or disfavoring by ASHP or its officers, directors or employees. The inclusion of any links to other sites does not imply a recommendation of such sites.

ASHP MAKES NO WARRANTIES OF ANY KIND, EXPRESS OR IMPLIED, AND DOES MAKES NO REPRESENTATIONS OR ENDORSEMENTS WITH RESPECT TO THE QUALITY, CONTENT, TIMELINESS, ACCURACY, COMPLETENESS, RELIABILITY, OR OWNERSHIP OF THE CONTENT, TEXT, GRAPHICS, LINKS OR OTHER ITEMS CONTAINED IN THIS RESOURCE, AND SPECIFICALLY DISCLAIMS ANY AND ALL SUCH LIABILITY. ANY RELIANCE PLACED ON SUCH INFORMATION IS AT THE SOLE RISK OF THE USER. IN NO EVENT WILL ASHP BE LIABLE FOR ANY LOSS OR DAMAGE, INCLUDING, WITHOUT LIMITATION, INDIRECT OR CONSEQUENTIAL LOSS OR DAMAGE, ARISING FROM THE USE OF THE RESOURCE.

Please direct any questions or feedback regarding this resource to newpractitioners@ashp.org. We appreciate your comments, feedback and suggestions as we strive to capture issues and challenges affecting New Practitioners.