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

2.) What is the recommended monitoring of LMWH in severe renal impairment?
   - Anti-factor Xa levels utilized as a surrogate biomarker of LMWHs anticoagulant effect
   - Anti-factor Xa levels do not need to be routinely monitored in most patients on LMWHs
   - 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 population
   - 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?

   **Dalteparin**
   - 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); if longer therapy needed, consider monitoring anti-factor Xa levels and adjust dose if accumulating
     - **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

   **Enoxaparin**
   - 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.
   - In patients with severe renal insufficiency who require therapeutic anticoagulation, the American College of Chest Physicians suggests the use of UFH instead of LMWH.
   - 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 levels.
   - Anti-factor Xa levels should be monitored and dose adjusted accordingly to maintain lab defined therapeutic range.
   - Avoid use of LMWH in severe renal insufficiency if anti-Xa levels cannot be monitored.
   - 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.
   - Capping doses of LMWH may be unsafe due to the risk of under-dosing in the obese patient.
   - Use of higher doses may lead to increased risk of bleeding.
   - There is uncertainty of when to obtain anti-factor Xa levels for monitoring.

2.) What is the recommended monitoring of LMWH in obese patients?
   - 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:** 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/day.
     - 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 dose.

Enoxaparin:
   - **Prophylaxis:** Clinical literature has recommended doses of Enoxaparin ranging from 0.5mg/kg SC Q12h or a 25% increase from the standard prophylaxis dose.
   - **Bariatric Surgery (Roux-en-Y gastric bypass):** BMI ≤50 kg/m²: 40 mg every 12 hours.
BMI >50 kg/m^2: 60 mg every 12 hours

- **Treatment:** 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

12. Smith J, Canton EM. Weight-Based Administration of Dalteparin in Obese Patients. AJHP. 2003;60(7):683-686

Other relevant references

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