Enoxaparin Dosing in Obese Patients

Shaun Moizuk
PharmD Candidate
Ohio Northern University

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Presentation Objectives

- Apply pharmacokinetic changes caused by obesity to enoxaparin dosing
- Explain pharmacology of enoxaparin
- Make dosing adjustments in obese patients undergoing enoxaparin therapy
Patient Case

- A 57 yof admitted to CCF on 08/29/10 for abdominal wall mass resection
- PMH: PE (post surgery 09’), morbid obesity, MI (04’), HTN, T2DM,
- Ht: 67”, Wt: 410lbs (186.4kg), Scr: 1.0
- IBW: 61.6kg, ABW: 111.5kg
- Est. CrCl (ABW): 109.3 ml/min
- H/H: 31.0/10.0, Plt: 172
- Allergies: none
Warfarin 10mg PO (dose adjusted by PCC)
NPH Insulin 10 units SQ hs
Metformin 1000mg PO bid
Pyridoxine (B-6) 100mg PO bid
Glipizide 10mg PO bid
Simvastatin 20mg PO hs
Atenolol 100mg PO daily
08/29/10: Pt admitted, UFH drip started
  - UFH used inpatient d/t concern of subtherapeutic anticoagulation with enoxaparin if done outpatient
09/01/10: Abdominal mass resection surgery
09/02/10: Erythema at incision site
  - Started cephalaxin 500mg PO q6h
09/04/10: Incision cellulitis/erythema worsened
  - Started vancomycin 1.5g IV q12h
- Continue pt on UFH drip to bridge to warfarin or send home on enoxaparin bridge?
Obesity = BMI ≥ 30 (morbid obesity ≥ 40)
Incidence increasing rapidly since 1980
More prevalent amongst minority populations
  - African American, Hispanic, Native American
Overweight
  - 32.2% of adults are overweight/obese
  - 17.1% of teenagers are overweight/obese
Morbid obesity
  - 2.8% of men and 6.8% of women [1]

Note: all statistics are from 2004
Obesity Pharmacologic Effects

- Increased Vd
  - Especially lipophilic drugs
  - Increased length of distribution phase

- CL remains largely unchanged
  - Adipose tissue has no intrinsic extraction properties
  - Primarily dependent on LBW [2]
FDA approved indications:
- ACS (UA, NSTEMI, STEMI)
- DVT/PE prophylaxis and treatment
  - Both inpatient and outpatient

MOA: inhibition of factor Xa
- Cannot catalyze thrombin-antithrombin reaction d/t short chain length (< 18 monosaccharides long)
- Higher ratio of factor Xa: factor IIa activity [3]
- PK/PD:
  - OOA: 3-5hrs
  - DOA: 12hrs
  - T1/2: 4.5-7hrs
- Vd: 4-6 liters (roughly equivalent to plasma volume)
  - Not a lipophilic drug
- Metabolism: Hepatic (desulfation, depolymerization)
- Excretion: Urine (40% unchanged) [3], [4]
Figure 11-1. Mechanism of action of UFH, LMWH, and fondaparinux. Abbreviations: UFH = unfractionated heparin; LMWH = low molecular weight heparin; AT = antithrombin; Xa = activated factor X.
- DVT/PE Prophylaxis: 30mg SQ bid OR 40mg SQ q daily
  - CrCl ≤ 30ml/min: 30mg SQ qd

- DVT/PE Treatment: 1mg/kg SQ bid OR 1.5mg/kg SQ q daily
  - CrCl ≤ 30ml/min: 1mg/kg SQ bid [4], [5]

- Maximum Dose: 150mg SQ bid (per CCF guidelines)
Enoxaparin Dose Monitoring

- Not usually needed unless:
  - Pt is obese
  - Pt has severe renal insufficiency [5]

- Anti-Factor Xa Levels
  - Measured 4 hours post 3rd or 4th dose
  - Goal ranges:
    - 0.2 – 0.4 units/ml (prophylaxis)
    - 0.6 – 1.0 units/ml (BID dosing, treatment)
    - 1-2 units/ml (Q Daily dosing, treatment) [5]
Enoxaparin Dosing Controversy

- Which weight to use for DVT/PE treatment dosing in obese patients?
- Should the dose be capped?
Dosing Weight Calculation Review

- **TBW:** Total body weight, in kg
- **IBW:** Ideal body weight
  - Men: 50kg + (2.3 x height in inches over 60”)
  - Women: 45.5kg + (2.3 x height in inches over 60”)
- **ABW:** Adjusted body weight
  - IBW + 0.4(TBW - IBW)
- **LBW:** Lean body weight (James formula) [7]
  - Men: \((1.10 \times \text{Weight(kg)}) - 128 \times (\text{Weight}^2/(100 \times \text{Height(m)})^2)\)
  - Women: \((1.07 \times \text{Weight(kg)}) - 148 \times (\text{Weight}^2/(100 \times \text{Height(m)})^2)\)
Dosing Weight Calculation Review

- Patient Case:
  - TBW: 186.4kg
  - IBW: 61.6kg
  - ABW: 111.5kg
  - LBW: 82.98kg
Enoxaparin DVT/PE Tx Dose in Obesity

- Enoxaparin distributes to the intravascular space
  - Vd closely tied to plasma volume
    - More dependant on IBW/LBW than TBW [9], [10], [11], [12]

- However, there is no cumulative anticoagulation effect with uncapped dosing
  - Obese patients up to 159kg dosed by TBW [13]

- Inverse correlation between anti-factor Xa levels and body weight
  - Obese pts might may not have proper anti-Xa levels [14]
96 patients stratified by weight to 3 groups
- BMI < 25 (32), BMI 25-29.9 (31), BMI ≥ 30 (33)

Tx = enoxaparin 1mg/kg (TBW) SQ bid for ACS/DVT OR enoxaparin 40mg SQ q daily for prophylaxis

Separated into 2 further groups after tx
- Bruising present (26) / bruising not present (70)
Results:
- BMI difference: $p = 0.14$
- Weight difference: $p = 0.632$
- CrCl difference: $p = 0.01^*$

Conclusion:
- No difference by weight/BMI in patients dosed similarly on enoxaparin
- Bleeding events tied more to CrCl than weight
Low-molecular weight heparins in renal impairment and obesity: available evidence and clinical practice recommendations [16]

- Expert review article covering 21 studies in the use of LMWH in DVT/PE treatment
- Examined obesity’s effects on pharmacokinetic/dynamics of LMWH in obese
- Created a set of recommendations for enoxaparin dosing in obese patients [16]
## Studies used by Nutescu et al in LMWH DVT/PE Dosing Recommendations

### EA Nutescu et al.

### Table 6b. Pharmacodynamic and Clinical Studies on Use of Treatment Doses of LMWH in Obese Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>LMWH (or comparator)</th>
<th>n/N^a</th>
<th>Dosing</th>
<th>Study Design</th>
<th>Definition of Obese</th>
<th>Anti-Xa levels</th>
<th>Outcome</th>
<th>Nonobese</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith (2003)^84</td>
<td>dalteparin</td>
<td>21</td>
<td>196.5 units/kg once daily</td>
<td>retrospective open-label</td>
<td>&gt;90 kg</td>
<td>mean</td>
<td></td>
<td>0.9 SD ± 1.1</td>
<td>1.1 SD ± 0.23</td>
</tr>
<tr>
<td>Yee (2000)^85</td>
<td>dalteparin</td>
<td>10/20</td>
<td>200 IU/kg/day or 120 IU/kg q12h</td>
<td>pharmacodynamic</td>
<td>BMI ≥30 kg/m^2</td>
<td>volume of distribution</td>
<td>8.36 (n = 10)</td>
<td>12.36 (n = 10; p = 0.11 vs nonobese)</td>
<td></td>
</tr>
<tr>
<td>Wilson (2001)^72</td>
<td>dalteparin</td>
<td>37</td>
<td>200 IU/kg once daily</td>
<td>prospective cohort</td>
<td>100–120% ideal body weight</td>
<td>mean</td>
<td></td>
<td>1.01 (95% CI 0.89 to 1.13) (n = 13)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>120–140% ideal body weight</td>
<td></td>
<td></td>
<td>0.97 (95% CI 0.85 to 1.09) (n = 14)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;140% ideal body weight</td>
<td></td>
<td></td>
<td>1.12 (95% CI 0.96 to 1.28) (n = 10)</td>
<td></td>
</tr>
<tr>
<td>Sanderink (2002)^86</td>
<td>enoxaparin</td>
<td>48</td>
<td>1.5 mg/kg sc once daily</td>
<td>pharmacodynamic</td>
<td>BMI 30–40 kg/m^2</td>
<td>(n = 24)</td>
<td></td>
<td>14–19% higher vs nonobese (n = 24; p &lt; 0.05)</td>
<td></td>
</tr>
<tr>
<td>Bazinet (2005)^87</td>
<td>enoxaparin</td>
<td>81/233</td>
<td>1.5 mg/kg once daily</td>
<td>prospective open-label</td>
<td>BMI &gt;30 kg/m^2</td>
<td>mean</td>
<td>1.13 (95% CI 1.04 to 1.22) (n = 28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 mg/kg bid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.15 (95% CI 1.02 to 1.25)</td>
<td></td>
</tr>
<tr>
<td>Hainer (2002)^87</td>
<td>tinzaparin</td>
<td>35</td>
<td>175 IU/kg</td>
<td>pharmacodynamic</td>
<td>100–160 kg</td>
<td>mean</td>
<td>0.87 (95% CI 0.78 to 0.96) (n = 28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.81 (95% CI 0.75 to 0.86)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>37</td>
<td>75 IU/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.30 (95% CI 0.28 to 0.32)</td>
<td></td>
</tr>
<tr>
<td>Barrett (2001)^48</td>
<td>tinzaparin</td>
<td>NA/425</td>
<td>175 IU/kg once daily</td>
<td>data analysis of 2 RCTs</td>
<td>BMI &gt;30 kg/m^2</td>
<td>LMWH clearance</td>
<td>22% decrease</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[^a]: Values are rounded to the nearest integer unless otherwise specified.
<table>
<thead>
<tr>
<th>Clinical outcomes</th>
<th>VTE treatment</th>
<th>VTE or major bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al-Yaseen et al. (2005)</td>
<td>193</td>
<td>retrospective chart review</td>
</tr>
<tr>
<td>enoxaparin (2001)</td>
<td>900</td>
<td>RCT</td>
</tr>
<tr>
<td>UFH</td>
<td>adjusted</td>
<td></td>
</tr>
<tr>
<td>RISTE registry Barba (2005)</td>
<td>294/8845</td>
<td>registry analysis</td>
</tr>
<tr>
<td>BMI &gt;26</td>
<td>BMI &gt;26</td>
<td></td>
</tr>
<tr>
<td>recurrent VTE</td>
<td>4.4%</td>
<td></td>
</tr>
<tr>
<td>major bleeding</td>
<td>7.3%</td>
<td></td>
</tr>
<tr>
<td>recurrent VTE</td>
<td>1.0%</td>
<td></td>
</tr>
<tr>
<td>major bleeding</td>
<td>1.3%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ACS</th>
<th>placebo</th>
<th>death, MI, UR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klein (1997)</td>
<td>13.3%</td>
<td>11.4%</td>
</tr>
<tr>
<td>FRISC</td>
<td>731/1497</td>
<td>RCT subgroup analysis</td>
</tr>
<tr>
<td>placebo</td>
<td>5.5%</td>
<td>4.0%</td>
</tr>
<tr>
<td>FRISC Investigators (1996)</td>
<td>3516/3481</td>
<td>adjusted doses</td>
</tr>
<tr>
<td>enoxaparin/UFH</td>
<td>death, MI, UR</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ischemic events or major bleeding</th>
<th>death, MI, UR</th>
</tr>
</thead>
<tbody>
<tr>
<td>death, MI</td>
<td>15.7%</td>
</tr>
</tbody>
</table>

ACS = acute coronary syndromes; BMI = body mass index; LMWH = low-molecular-weight heparin; MI = myocardial infarction; NA = not available; OR = odds ratio; RCT = randomized clinical trial; UFH = unfractionated heparin; UR = urgent revascularization; VTE = venous thromboembolism.

*n/N = obese patients/total study population. If the total study population included only obese patients, just 1 number is given.
Enoxaparin Dosing Recommendations based on Nutescu et al. Article

- Monitoring not needed in obese pts unless:
  - Weight \( \geq 190 \text{kg} \)
  - Adjust dose in these patients based on anti-factor Xa

- Only use BID dosing in obese patients

- Created a dosing nomogram based on anti-factor Xa levels [16]
# Anti-Factor Xa Based Enoxaparin Dose Adjustment

<table>
<thead>
<tr>
<th>Anti-Xa Level (U/mL)</th>
<th>Hold Next Dose</th>
<th>Dosage Change</th>
<th>Next Anti-Xa Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.35</td>
<td>no</td>
<td>increase by 25%</td>
<td>4 h after next dose</td>
</tr>
<tr>
<td>0.35–0.49</td>
<td>no</td>
<td>increase by 10%</td>
<td>4 h after next dose</td>
</tr>
<tr>
<td>0.5–1.0</td>
<td>no</td>
<td>no</td>
<td>next day, then in 1 wk, then monthly</td>
</tr>
<tr>
<td>1.1–1.5</td>
<td>no</td>
<td>decrease by 20%</td>
<td>before next dose</td>
</tr>
<tr>
<td>1.6–2.0</td>
<td>3 h</td>
<td>decrease by 30%</td>
<td>before next dose and 4 h after next dose</td>
</tr>
<tr>
<td>&gt;2.0</td>
<td>until anti-Xa &lt;0.5 U/mL</td>
<td>decrease by 40%</td>
<td>before next dose and q12h until anti-Xa &lt;0.5 U/mL</td>
</tr>
</tbody>
</table>

LMWH = low-molecular-weight heparin.
Reproduced from Monagle et al. *Chest* 2001;119(suppl 1):344-70, with permission from the American College of Chest Physicians, adapted according to Nutescu et al.²
09/07/10: Pt given enoxaparin 150mg SQ bid
  - Delay d/t insurance coverage issues with dose
Anti-factor Xa measured 6hrs after 1st dose
  - Anti-factor Xa was 0.3 units/ml (within-range)
09/07/10: D/c'd home on enoxaparin bridge to warfarin and PO bactrim after cellulitis resolution
F/u on enoxaparin completed over phone by CCF pharmaceutical care clinic (PCC)
- Use standard bid enoxaparin dosing in obese patients based on TBW for DVT/PE tx
  - Data only exists on enoxaparin up to 150kg
    - Maximum dose of 150mg/kg

- Monitor anti-factor Xa levels in pts who are morbidly obese (BMI ≥ 40)
  - Adjust dose based on anti-factor Xa level


