SURGICAL GRAND ROUNDS
March 17th, 2007

Low Molecular Weight Heparin for Prevention and Treatment of Venous Thromboembolic Disorders

Guillermo Escobar, M.D.
LMWH vs UFH

Jayer’s sales pitch:
LMW is expensive and not better than UFH

FALSE
What are these Heparins?

- Heparin was discovered over 90 years ago.
- Binds AT III to accelerate 1000 x its irreversible inactivation of Thrombin (also Xa, IX + XII)
- UFH is a large, heterogeneous mixture of glycosaminoglycans (MW 3000-30,000) that bind to antithrombin via a pentasaccharide
- Only 1/3 of it actually binds to AT III!
- UFH also binds to endothelial cells, platelet factor 4, platelets, increases vessel wall permeability, suppresses the vascular smooth muscle cells, suppresses osteoblast formation, and activates osteoclasts = Osteopenia
What are these Heparins?

- LMWH weigh 4000-5000 daltons
- They affect Xa more than II (2-4 times).
- Less binding to Mϕ and endothelial cells to increase their half-life
- LOWER bone loss
- Renal excretion, therefore in the obese and renally impaired Xa activity should be monitored.

1. Up to 31% of patients treated with UFH will have thrombocytopenia.

2. Pts treated with UFH will form antibodies vs. platelet factor-4 (PF4) - heparin complexes in 17% vs. 8% of LMWH

3. Once formed, exposure to subsequent heparin (flushes, central lines etc) may suffer thrombocytopenia, thrombosis, bleeding, limb loss and/or death. The historic M+M was 16% and 23%!

4. 89% of patients with HIT are from surgical services! (PF4 release from activated platelets during surgical trauma)

5. There were 7,786,390 (20% of all discharges) surgical inpatients in 2003. 41% were high of very high risk for VTE events. An equal number were medical patients at risk.

6. Hospital stay during conversion from IV to oral anticoagulation and/or “bridging” can take weeks ($$$$)!

Why invent LMWH?

7. UFH requires painful and costly PTT, in addition to INR.
8. PTT is variable and varies significantly from institution to institution. “Variations are such that ... a hospital would achieve a much different degree of heparinization from year to year.”

### TABLE 1. Risk Factors Observed in 1231 Consecutive Patients Treated for Acute DVT and/or PE

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥40 years</td>
<td>88.5</td>
</tr>
<tr>
<td>Obesity</td>
<td>37.8</td>
</tr>
<tr>
<td>History of venous thromboembolism</td>
<td>26.0</td>
</tr>
<tr>
<td>Cancer</td>
<td>22.3</td>
</tr>
<tr>
<td>Bed rest ≥5 days</td>
<td>12.0</td>
</tr>
<tr>
<td>Major surgery</td>
<td>11.2</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>8.2</td>
</tr>
<tr>
<td>Varicose veins</td>
<td>5.8</td>
</tr>
<tr>
<td>Fracture (hip or leg)</td>
<td>3.7</td>
</tr>
<tr>
<td>Estrogen treatment</td>
<td>2.0</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.8</td>
</tr>
<tr>
<td>Multiple trauma</td>
<td>1.1</td>
</tr>
<tr>
<td>Childbirth</td>
<td>1.1</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.7</td>
</tr>
</tbody>
</table>

1 or more risks    96.3
2 or more risks    76.0
3 or more risks    39.0
Risk Factors for Venous Thromboembolism

Moderate Risk factors (OR 2-9)

- Arthroscopy, Central venous lines, Chemotherapy, CHF, HRT, malignancy, OCP, Paralytic stroke, pregnancy/postpartum, Previous DVT/PE, Thrombophilia

Circulation. 2003 Jun 17;107(23 Suppl 1):I9-16

1. Higher risk surgery: LDUH (5,000 U tid) or LMWH (> 3,400 U daily) [both Grade 1A].
2. High-risk surg + multiple risk factors: combine LDUH TID or LMWH > 3,400 U daily) + compression stockings and/or SCDs (Grade 1C+).
3. Hip Fracture surgery: LMWH at high-risk dose (grade 1C+)
4. Trauma and spinal chord injury: LMWH prophylaxis as soon as considered safe (Grade 1A)
DVT/PE Prevention


5. High risk critically ill patients: LMWH!
6. Travel >6hrs with risk factors: “LMWH, injected prior to departure” – NOT aspirin~!
TREATMENT of DVT

Evaluation of 15 meta-analysis that pooled data of all RCT comparing LMH vs UFH

- LMWH had fewer episodes of major bleeding than those treated with UFH.
- All but 1 of 10 reviews showed LMWH significantly reduced mortality in 3 to 6 months of FU.
- 32-57% cost saving with LMWH use as an inpatient for treatment of DVT/PE, particularly if quality-adjusted life-years was included.
- Globally cheaper if only 8% of patients with DVT/PE are treated as outpatients!

Level 1 evidence
Cochrane Review - LMWH vs. UFH for Rx VTE

- Reviewed 22 RCT totaling >8,800 patients, 95% CI
- Thrombus size was reduced in 53% vs. 45% in LMWH (CI 0.59 to 0.81)
- Major bleeding 1.2% vs. 2% (CI 0.39 to 0.83)
- Lower overall mortality (3.3% vs. 5.3 - CI 0.46 to 0.84)

Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism
Cochrane Database of Systematic Reviews Issue 4, 2004
Cochrane Review (+) LMWH vs. UFH for Rx VTE in oncology

- Reviewed 15 RCT 95% CI
- Lower overall mortality (RR) = 0.71; CI 0.52 to 0.98
- Daltaparin alone = 52% reduction in symptomatic, recurrent VTE (17% vs. 9%, $p = 0.002$)

Anticoagulation for the initial treatment of venous thromboembolism in patients with cancer. Cochrane Database of Systematic Reviews Issue 1, 2008
Comparison of fixed-dose weight-adjusted unfractionated heparin and low-molecular-weight heparin for acute treatment of venous thromboembolism.


- 697 patients prospectively treated with UFH vs. LMWH
- Recurrence occurred in 13 UFH (3.8%) vs. 12 with LMWH (NS).
- Major bleeding in the first 10 days 4 vs. 5 (NS).
- Treatment out of hospital in 72% of UFH group vs. 68% of LMWH.
Even with a 5000U/mL heparin vial, to give 333U/kg loading + 250U/12hrs would require the "70kg" male to get 4-5cc SQ every 12hrs!
WAKE UP
Conclusions

1. LMWH decrease the risk of bleeding
2. LMWH decrease the risk of HIT/HITT
3. LMWH are clinically equally or BETTER to reduce the risk of DVT/PE in prophylaxis
4. LMWH are easier/predictable to manage than UFH (no testing)/blood samples – Guidelines are not followed!
5. LMWH lead to earlier discharge for TREATMENT of DVT/PE
6. LMWH decrease the cost of treatment of venous thrombotic events – (Canadian camels not withstanding)
7. All the above is ACCP guideline + Cochrane review supported
8. Safer than warfarin for long-term use*

*Cochrane Database of Systematic Reviews 2008 Issue 1
Thank you