LOW MOLECULAR WEIGHT HEPARIN DOSING AND MONITORING GUIDELINE

PURPOSE:
To provide standardized dosing and monitoring guidelines for patients receiving low molecular weight heparin (LMWH) therapy.

The guidelines provided below are recommendations to assist the medical staff in appropriate administration and monitoring of LMWH therapy. The final decision by the medical staff to follow the guidelines is left to their discretion. However, documentation of this decision is recommended.

GUIDELINE

1. Laboratory Monitoring
   a. The following baseline laboratory tests should be ordered for all patients prior to receiving therapeutic and long-term prophylaxis with anticoagulant medications. These labs should also be considered in patients receiving short-term prophylaxis if additional risk factors are present. Results should be reviewed prior to initiation of LMWH therapy whenever possible.
   - Prothrombin Time (PT)
   - Activated Partial Thromboplastin Time (aPTT)
   - CBC with differential count
   - Fibrinogen
   - Additional testing including antithrombin level should be performed in consultation with hematology.
   - Consider other tests, in consultation with hematology, for evaluation of thrombophilic disorders as clinically indicated prior to initiation of LMWH therapy.

   b. LMWH therapy should be monitored with “LMWH Level” within Epic.
   - LMWH levels correspond to anti-factor Xa levels in Epic and should be ordered as “LMWH Level.” This allows for the correct level to be ordered, so it is not confused with the UFH Level (which is also an anti-factor Xa level, but run for UFH instead of LMWH).

   c. The LMWH Level should be checked 4 to 6 hours following the subcutaneous (SC) administration of a dose.
   - Draw the LMWH level from a fresh venipuncture so there is NO CONTAMINATION from standard heparin left in the IV line tubing.
     1. Contamination would be indicated by an elevated aPTT drawn simultaneously with the LMWH level.
d. **Goal LMWH Levels are as follows:**
   - **Goal Treatment LMWH Levels** (drawn 4 to 6 hours following any dose) = 0.5 – 1 units/ml (in patients receiving Q12hour therapy)
   - **Goal Prophylactic LMWH Levels** (drawn 4 to 6 hours following any dose) = 0.1 – 0.3 units/ml

e. **Trough LMWH Levels:** Use of a trough LMWH level may be considered in patients with severe renal dysfunction (CrCl < 30 ml/min). Trough levels are used only to assess bleeding risk. If the trough is < 0.3 units/ml, no action or change in therapy is indicated. No data exists to assess therapeutic efficacy based on trough LMWH levels. To assess efficacy, peak levels (4 to 6 hours following a dose) should be utilized.

2. **Initial Dosing**
   a. See Table 1, “Recommendations for Enoxaparin Dosing and Monitoring” for initial dosing recommendations.
   
   b. LWMH should be administered via subcutaneous (SC) injection. However, in the neonatal population, intravenous (IV) administration is acceptable.
   
   c. Enoxaparin is the LMWH of choice at CCHMC. If a patient receives a LMWH other than enoxaparin, modify dosing according to the manufacturer’s product information for that specific medication.
   
   d. Commercially available unit dose sized products should be used whenever available.
      - Commercially available enoxaparin syringe sizes include:
        o Non-graduated, prefilled syringes: 30 mg, 40 mg
        o Graduated, prefilled syringes: 60 mg, 80 mg, 100 mg, 120 mg and 150 mg
   
   e. All doses at CCHMC will be dispensed using a 100 mg/ml commercially available product.
      - Inpatient: Doses less than 20 mg will be drawn up in a ½ ml Tuberculin syringe with needle attached.
      - Outpatient: Doses less than 20 mg will use an insulin syringe, with teaching provided to the family on the proper technique to draw up and administer the medication.
# Table 1. Recommendations for Enoxaparin Dosing and Monitoring

<table>
<thead>
<tr>
<th>Patient Type/Age</th>
<th>Enoxaparin Dosing</th>
<th>LMWH Level Monitoring Frequency</th>
<th>Comments/Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>&lt;1 year</strong></td>
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</tr>
<tr>
<td>Prophylaxis</td>
<td>0.75 mg/kg/dose Q12hrs SC</td>
<td>Not recommended</td>
<td>After 2rd dose and weekly to monthly after therapeutic dose achieved</td>
</tr>
<tr>
<td>Treatment</td>
<td>1.5 mg/kg/dose Q12hrs SC [Max dose = 2 mg/kg]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1 year to 18 years or ≤ 50 kg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>0.5 mg/kg/dose Q12hrs SC</td>
<td>Not recommended</td>
<td>After 2nd dose and weekly to monthly after therapeutic dose achieved</td>
</tr>
<tr>
<td>Treatment</td>
<td>1 mg/kg/dose Q12hrs SC [Max dose = 2 mg/kg]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>&gt;18 years or &gt;50 kg</strong></td>
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<tr>
<td>Prophylaxis</td>
<td>40 mg once daily or 30 mg Q12hr SC</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Treatment</td>
<td>1 mg/kg/dose Q12hr SC [Max dose = 150 mg Q12hrs]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Renal Dysfunction (CrCl&lt;30ml/min)</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Consider decreasing dose</td>
<td>1 mg/kg/dose Q24hrs SC [Alternative dose: 0.5 mg/kg/dose Q12hrs SC]</td>
<td>Consider monitoring, but not recommended</td>
<td>After 2nd dose and weekly to monthly after therapeutic dose achieved</td>
</tr>
<tr>
<td><strong>Pregnancy</strong></td>
<td>40 mg once daily or 30 mg Q12hrs SC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prophylaxis</td>
<td></td>
<td>Not recommended</td>
<td>After 2nd dose and weekly to monthly after therapeutic dose achieved</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*Some references recommend a prophylaxis dose of 0.5 mg/kg/dose Q12hrs and a treatment dose of 1 mg/kg/dose Q12hrs for patients 2 months to 1 year of age. However, these lower doses often do not achieve therapeutic LMWH levels, so CCHMC recommends the higher starting dose for all patients less than 1 year of age.*
3. **Dose Titration of LMWH Therapy**

LMWH therapy should be adjusted based on LMWH levels. Enoxaparin therapy should be adjusted as described in Table 2.

LMWH levels should be verified for correct draw times (4 to 6 hours after any dose) and no contamination (see 1C above). Contamination would be indicated by an elevated aPTT drawn simultaneously with the LMWH level.

a. When modifying enoxaparin doses, commercially available unit dose sized products should be used whenever available (see 2C above).

<table>
<thead>
<tr>
<th>LMWH Level</th>
<th>Dose Change</th>
<th>Repeat LMWH Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.35 units/ml</td>
<td>Increase dose by 25%</td>
<td>4-6 hours following new dose</td>
</tr>
<tr>
<td>0.35-0.49 units/ml</td>
<td>Increase dose by 10%</td>
<td>4-6 hours following new dose</td>
</tr>
<tr>
<td>0.5-1 units/ml</td>
<td>No changes</td>
<td>Weekly to Monthly at 4-6 hours following dose</td>
</tr>
<tr>
<td>1.1-1.5 units/ml</td>
<td>Decrease dose by 20%</td>
<td>4-6 hours following new dose</td>
</tr>
<tr>
<td>1.6-2 units/ml</td>
<td>Decrease dose by 30%</td>
<td>4-6 hours following new dose</td>
</tr>
<tr>
<td>&gt;2 units/ml</td>
<td>Hold all further doses • Measure LMWH level Q12hrs until level is 0.5 units/ml • Restart enoxaparin at a dose 40% less than what was originally prescribed</td>
<td></td>
</tr>
</tbody>
</table>

4. **Monitoring of therapy, precautions and ongoing follow-up:**

a. Measure platelet counts regularly (minimum of once every 2 weeks) while a patient is receiving LMWH therapy. Suspect heparin-induced thrombocytopenia (HIT) if platelet count drops below 150 x 10^9/L.
   - The risk of HIT is rare with LMWH therapy, but can occur.

b. Consider bone densitometry studies at baseline and then at regular intervals (approximately every 12 months) in patients expected to be on long-term LMWH therapy (>3 months).

c. Avoid intramuscular (IM) injections and arterial punctures during LMWH therapy. If arterial punctures are warranted, consider appropriate precautions, including the use of extended period of external pressure.

d. Avoid aspirin and other antiplatelet drugs during LMWH therapy. If analgesia is required, acetaminophen is the preferred drug.
e. For patients having a lumbar puncture, delay the lumbar puncture until 2 consecutive doses of LMWH have been held (at least 18 hours from last injection). Do NOT use LMWH in patients receiving continuous epidural anesthesia.
  • Perispinal hematomas and paralysis have been reported in patients having a lumbar puncture while receiving LMWH.

5. **LMWH Discontinuation and Reversal**

a. It is recommended to discontinue LMWH 24 to 26 hours prior to surgical procedures. Give the last dose of LMWH in the morning of the day before the procedure.

b. If anticoagulation with LMWH needs to be discontinued for clinical reasons, such as bleeding, termination of the subcutaneous injection will usually suffice.

c. If an immediate reversal effect is required, IV *protamine sulfate* has NOT been shown to completely reverse LMWH. Increased microvascular bleeding produced by very high concentrations of LMWH is neutralized by protamine sulfate.

   • The dose of protamine sulfate is dependent on the dose of LMWH used and the time of administration. If protamine sulfate is given within 3 to 4 hours of LMWH, then a maximal neutralizing dose is 1 mg of protamine sulfate per 100 units (1 mg) of LMWH given in the last dose.

   • Protamine should be administered within 4 hours of a LMWH dose. If administered significantly beyond 4 hours after a LMWH dose, protamine sulfate may cause an increased risk of bleeding.

   • Protamine sulfate should be administered intravenously and over a 10 minute period, as rapid infusion can cause hypotension.

   • Patients with known hypersensitivity to fish, and those who have received protamine-containing insulin or previous protamine therapy may be at risk of hypersensitivity reactions to protamine sulfate.

6. **Duration of Therapy**

a. It is recommended to refer a patient to a specialist for the ongoing outpatient management of LMWH therapy.
b. The duration of LMWH therapy is dependent on patient indications.

c. CCHMC sponsors a Thrombophilia Program that manages patients receiving LMWH (Phone: 513-636-6213).

7. Transitioning LMWH Therapy

LMWH should be transitioned to and from other anticoagulant medications as listed below.

Table 3. Transitioning LMWH Therapy

<table>
<thead>
<tr>
<th>Transitioning Medication</th>
<th>Stop Current Medication</th>
<th>Start New Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMWH to UFH*</td>
<td>Stop LMWH after UFH initiation</td>
<td>Start UFH 4 hours after the last LMWH dose. No UFH bolus required if started 4 hours after last LMWH dose. Note: If UFH started &gt;12 hours following last LMWH dose, an UFH bolus dose is indicated.</td>
</tr>
<tr>
<td>UFH to LMWH</td>
<td>Stop UFH Zero to 4 hours after first LMWH dose</td>
<td>Start LMWH when clinically indicated</td>
</tr>
<tr>
<td>LMWH to Warfarin</td>
<td>Stop LMWH after a minimum of 2 consecutive therapeutic INRs</td>
<td>Start warfarin when clinically indicated and patient able to tolerate medication</td>
</tr>
<tr>
<td>Warfarin to LMWH</td>
<td>Stop warfarin when clinically indicated or 5 days prior to procedure</td>
<td>Start LMWH within 24 hours of holding warfarin*</td>
</tr>
</tbody>
</table>

*UFH = Unfractionated heparin

*Patients with a higher clotting risk may be started on LMWH immediately upon the discontinuation of warfarin.

8. LMWH Background Information

Low molecular weight heparins (LMWHs) have rapidly become the anticoagulant of choice in pediatric patients, despite their undocumented efficacy. Enoxaparin is frequently the LMWH of choice in children, as the majority of available data is based upon this agent.

LMWHs are prepared from unfractionated heparin (UFH) by enzymatic or chemical hydrolysis. LMWH inhibits factor Xa more potently than thrombin, whereas UFH predominantly inhibits thrombin.
The potential advantages of LMWH for pediatric patients include the need for minimal monitoring, lack of interference by other drugs or diet, reduced risk of heparin-induced thrombocytopenia (HIT), and the probable reduced risk of osteoporosis with long-term use. Bleeding remains the main complication of LMWH therapy.

REFERENCES