Enoxaparin
Updated November 2016

Enoxaparin is a low-molecular weight heparin (LMWH). Because of its lower protein-binding compared to unfractionated heparin (UFH), enoxaparin has more predictable pharmacokinetics and less need for therapeutic monitoring. Enoxaparin is frequently used as prophylaxis for deep venous thrombosis (DVT) in critically ill human patients. The ideal prophylactic regimen in critical care patients is still unclear and remains highly investigated. Individual patient factors (such as BMI and renal function) alter drug metabolism and, therefore, serum drug level monitoring to achieve a target anti-Xa factor blood level is ideal in higher risk patients. The availability of drug monitoring is poor and impractical in most veterinary settings. Thus recommendations for dose, route, and interval of administration in veterinary patients are extrapolated from those used in human patients. The ideal application, dosing guideline, and safety in veterinary patients remain unknown.

**Mechanism of Action:**
Heparin and LMW-heparins prevent clot formation by binding antithrombin. The heparin-antithrombin complex can then bind to and inactivate either thrombin (Factor II) or activated-Factor Xa. Low-molecular weight heparin will only bind and inactivate activated Factor Xa.

**Derivation and Metabolism:**
- Derived from heparin to yield fragments one third the size of heparin. Mean LMWH size: 4500-5000 Da
- Metabolism: Hepatic metabolism via breakdown to less biologically active molecules. Approximately 10% of the active drug is renally excreted.
- Maximum anti-Xa and anti-thrombin activity occurs 3-5 hours after administration. Steady state achieved after 24 hours of therapy
- Elimination half-life 4.5 hours (single dose) or 7 hours (repeated doses)

**Benefits of LMWHs:**
- Lower binding properties than unfractionated heparin (UFH). Reduced binding to plasma proteins and cells is responsible for the more predictable dose-response
- Reduced ability to inactivate thrombin (Factor II) because the smaller fragments cannot bind simultaneously to antithrombin (AT) and thrombin
- Nearly equal ability to inactivate factor Xa as heparin, despite smaller molecule size
- Longer plasma half-life (compared with UFH)
- Lower risk of heparin-induced thrombocytopenia and osteopenia

**Dosing Suggestions/Guidelines:**
- 1 mg/kg SQ q12hrs – preferable dosing regimen unless renal disease, obesity, or emaciation
  - Consider reduction of dose in the above patient population (0.7 mg/kg BID OR 1 mg/kg SID)
- 0.8 mg/kg SQ q6hrs also reported in a recent case series of IMHA dogs – no bleeding complications noted
- Significant anti-Xa activity persists for > 12 hours. Maximum anti-Xa and anti-IIa activity 3-5 hrs post dose
- No consensus exists regarding continued dosing and tapering after discharge from the hospital. Consider reducing frequency to q24hrs for 7-10 days before stopping dosing at home
Patient Selection:

Labeled indications: (humans)
- Prophylaxis of DVT in abdominal surgery, orthopedic/joint replacement surgery, immobility due to critical illness
- Treatment of acute DVT +/- concurrent PTE
- Ischemic myocardial disease/myocardial infarction

Extra-label/Theoretical indications:
- IMHA
- Pancreatitis, postop venotomy (invasive adrenal tumors), ischemic organ injury/postop torsion, portal vein thrombosis (PVT)
- Arterial embolic disease, protein-losing diseases (platelet inhibitors are preferred)

Contraindications for enoxaparin use
- Coagulopathy, patient considered ‘high risk’ for bleeding complications due to underlying illness
- Hypersensitivity to heparin or pork products
- Heparin-induced thrombocytopenia (Ab-mediated)
- Impending invasive surgical procedure, CSF tap, etc.

High-risk patients - consider dose reduction vs. interval reduction
- Renal disease (azotemia, oliguria); mild CKD probably ok → reduce to 1 mg/kg SID
- Obese patients; dose reduction to 0.7-0.8 mg/kg BID

Adverse effects per product label in 1% of patients:
- bleeding, anemia, thrombocytopenia, ALT/AST, diarrhea, nausea

Patient Monitoring:
- Therapeutic drug level monitoring via anti-Xa level can be performed but are impractical. PTT levels are prolonged with use but it is hard to extrapolate anti-Xa levels from PTT
- Dosing and clinical efficacy are empirical and presumptive
- Reassess patient stability and risk factors for complication DAILY
  - Bleeding complications?
  - New azotemia/AKI?
  - Potential need for invasive procedure with bleeding risk?
  - If concerns about bleeding/bruising or renal insufficiency, reduce dose to 0.7-0.8 mg/kg BID and continue to reassess
  - Avoid acute discontinuation given risks of rebound hypercoagulability

Product Formulation:
- Commercially available single-use auto-injector pens. Must be prescribed from a human pharmacy
  - 100 mg/ml – multiple sizes (0.3ml, 0.4ml, 0.6ml, 0.8ml, 1ml)
  - 150mg/ml – two sizes (0.8ml, 1ml)
- Currently this medication is NOT stocked at Ethos East hospitals through regular inventory channels
- The IVG Compounding Pharmacy carries 2 syringe sizes of the 100mg/ml concentration
  - 100mg/ml: 30 mg (0.3 ml; $40) and 100mg (1ml; $80)
  - Send a prescription to the IVG compounding pharmacy as for any other medication. Indicate the size syringe (0.3ml or 1ml) and number of syringes desired
  - Due to pharmacy regulations, the compounding pharmacy CANNOT transfer the medication within the syringes into any other container (see below).
- Each injection administered should have a “Misc Injection” fee (i390) charged ($18.63) to the client
**Preparation and Administration:**
- Confirm your desired prescription pen volume and concentration!
- Swab the top of a sterile rubber-stoppered, no-additive glass vial with alcohol
- Empty entire pen content into the glass vial into a by firmly pressing the rubber cap of the pen to the stopper top and compressing the yellow plunger
  - The needle protected by the rubber cap will protrude through the cap and puncture the glass vial, emptying its contents into the vial. Discard entire spent pen in a sharps container.
- LABEL the glass vial using the prescription label from the drug (tape onto vial)
  - Ensure the concentration, drug type, and date are clearly labeled
- Draw desired dose from the glass vial using aseptic technique – do NOT open the vial. Given that the vial is now intended for multiple uses, sterility/cleanliness is essential.
- Store at room temperature.
- Because the syringes are intended for single use in humans, handling/transfering the medication in this way is considered off-label.

**Example:**
An 8.0 kg West Highland White Terrier is recovering from a right adrenalectomy that necessitated a caval venotomy for tumor and clot evacuation.
- Dose: 1 mg/kg SQ BID of enoxaparin for clot prophylaxis.
- 8 mg dose using 100 mg/ml vial $\rightarrow$ 0.08 ml (8 units using U-100 syringe for accurate dosing) SQ BID

No consensus exists regarding continued dosing and tapering after discharge from the hospital.
- Consider reducing frequency to q24hrs for 7-10 days before stopping dosing at home
- Consider concurrent use of clopidogrel at home.

**References:**