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OPTIMIZING ENOXAPARIN THERAPY: DOSING GUIDELINES

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Enoxaparin (Lovenox®) is the UIHC formulary low molecular weight heparin (LMWH). Like heparin, enoxaparin exerts its action via binding with antithrombin III to ultimately inhibit crucial steps in the clotting cascade; unlike heparin, however, enoxaparin inhibits factor Xa and IIa (thrombin) to different extents. Heparin inhibits these clotting factors in a 1:1 ratio while enoxaparin does so in a 4:1 ratio. Enoxaparin also has improved bioavailability compared with heparin. These features contribute to more predictable pharmacokinetic properties.¹

Enoxaparin is commonly prescribed for prevention and treatment of thromboembolic events including those associated with knee and hip replacement, hip fracture, major surgery including abdominal surgery and neurosurgery, unstable angina, and general decreased mobility in medical and surgical patients. Since enoxaparin's marketing in 1995, its efficacy has been repeatedly demonstrated in multiple clinical trials for numerous clinical indications. This article will summarize current dosing and monitoring information.

Once-Daily Dosing

Although the original product labeling recommended twice-daily dosing for all indications, **once-daily dosing of enoxaparin has since been studied and been found to be as safe and effective as twice-daily administration for specific indications and is now included in the product labeling.**²⁻⁸ UIHC endorses once-daily enoxaparin dosing when therapeutically appropriate. In addition to being less costly than twice-daily dosing, once-daily administration spares patients additional injections, is simpler, and saves on nursing time.

Based on the 2004 CHEST Guidelines⁶⁻⁷ and current product labeling,⁵ Table 1 contains recommended enoxaparin doses to help guide prescribing.

Renal Insufficiency

Renal insufficiency (CrCl < 30 mL/min) necessitates special consideration. According to the enoxaparin product labeling, "in patients with severe renal impairment, the AUC at steady-state is increased by 65% after repeated doses compared to healthy volunteers after repeated subcutaneous (SQ) 40 mg once-daily doses."⁵ Across prophylactic indications for patients with renal insufficiency, all FDA-labeled doses are 30 mg SQ daily. For treatment of a venous thromboembolism, the 2004 CHEST Guidelines recommend use of unfractionated heparin.¹ If enoxaparin is used for treatment, the FDA-labeled dose is 1 mg/Kg SQ daily although some sources recommend even lower mg/Kg doses.⁹⁻¹¹ Monitoring anti-factor Xa levels should be considered when anticipating longer (> 1 week) treatment doses in patients with renal insufficiency.



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Table 1: Enoxaparin Dosing Strategies

INDICATION	CrCl ≥ 30 mL/min	CrCl < 30 mL/min
Prophylaxis		
General medical patients [§]	Enoxaparin 40 mg SQ daily	Enoxaparin 30 mg SQ daily [§]
Ischemic stroke with impaired mobility		
General surgery patients at moderate to high risk* [§]		
Neurosurgery and acute spinal cord injury		
Hip replacement or fracture surgery [§]		
Knee replacement surgery	Enoxaparin 30 mg SQ q12h	
Trauma with additional risk factors*		
Treatment		
Deep venous thrombosis ± pulmonary embolism treatment [§]	Enoxaparin 1.5 mg/Kg SQ daily [‡]	Intravenous heparin (preferred) [†]
Unstable angina or non-Q-wave myocardial infarction	Enoxaparin 1 mg/Kg SQ q12h [‡]	OR Enoxaparin 1 mg/Kg SQ daily [§]

SQ = subcutaneous; CrCl = creatinine clearance

[§] FDA-approved, once-daily dosing

* Venous thromboembolism (VTE) risk factors: advancing age, bed rest or immobilization, heart failure, previous VTE, obesity, malignancy, chronic obstructive pulmonary disease, estrogen use, and thrombophilias.

[†] The 2004 *CHEST* Guidelines recommend using intravenous unfractionated heparin for full therapeutic anticoagulation in patients with severe renal insufficiency.

[‡] Please round to the nearest syringe size. Available sizes include: 30 mg, 40 mg, 60 mg, 80 mg, 100 mg, 120 mg, and 150 mg

Obesity

Data on dosing obese patients, particularly those over 150 Kg, are limited. For prophylaxis in patients with a body mass index (BMI) ≥ 50 Kg/m², Scholten et al. suggest a 25% increase in dose (e.g., enoxaparin 40 mg SQ every 12 hours as opposed to 30 mg SQ every 12 hours).¹² For treatment, doses may be capped at 150 mg SQ every 12 hours; however, there are no available data to support this regimen. Because the volume of distribution in obese patients may vary, it may be useful to begin with enoxaparin 150 mg SQ every 12 hours and obtain anti-factor Xa levels to assess therapy in those heavier than 150 Kg.

Anti-Factor Xa Levels

Note that **aPTT levels are of no use in monitoring enoxaparin**. Monitoring of anti-factor Xa levels is still somewhat controversial. Patients to consider for anti-factor Xa level monitoring are those who are low-weight (< 45 Kg) or overweight (> 150 Kg or BMI ≥ 50 Kg/m²). For venous thromboembolism treatment in patients with renal insufficiency (CrCl < 30 mL/min), the 2004 *CHEST* Guidelines strongly recommend using intravenous unfractionated heparin as opposed to enoxaparin; however, if enoxaparin is used, the authors also suggest checking an anti-factor Xa level.¹ Primary literature articles lend support to this practice.¹²⁻¹⁸ During the 4-to-6-hour window after a SQ dose, the therapeutic enoxaparin range, expressed as anti-factor Xa activity, is 0.7-1.3 anti-Xa units/mL while the prophylactic range is 0.3-0.7 anti-Xa units/mL. Despite these ranges, **there are no reputable published recommendations on enoxaparin dosage adjustment following a sub- or supratherapeutic anti-factor Xa level. Please consider the necessity of this assay, how it will be interpreted, and anticipated duration of enoxaparin prior to ordering an anti-factor Xa level as it will take four days to return.**

Dose Rounding

Enoxaparin is available as commercially packaged syringes in several strengths including 30 mg, 40 mg, 60 mg, 80 mg, 100 mg, 120 mg, and 150 mg sizes. To help minimize cost (see Table 1) and the potential for an administration error, it is recommended that the dose be rounded to the nearest available syringe size.

Summary

Enoxaparin constitutes a major advance in therapy over intravenous unfractionated heparin as it needs less monitoring, has a lesser likelihood of predisposing patients to bleeding complications, and is easier to continue in the outpatient setting. However, it also has risks – particularly accumulation in patients with renal compromise. The proper dose in patients with renal insufficiency, while better defined today than several years ago, continues to be studied, and adequate dosing in obese patients is only starting to be examined. Additional studies are needed to determine precise recommendations for dosing in these populations. The Pharmacy serving your patient care area or the Drug Information Center (6-2600) can assist in answering these questions.

More detailed information regarding enoxaparin dosing and monitoring and the management of venous thromboembolic events can be found at:

- Preventing and Treating Thromboembolism in the 21st Century. Cleveland Clinic Journal of Medicine. 2005; 72:Supplement 1. <http://www.ccm.org/toc/Thromboembolism.htm>
- The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence-Based Guidelines. Chest. 2004; 126:Supplement 3. <http://www.chestjournal.org/>

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1. CHEST. 2004; 126:S188-203.
2. Ann Intern Med. 2001; 134:191-202.
3. Ann Surg. 2001; 233:438-44.
4. J Trauma. 2003; 54:1111-5.
5. Lovenox package insert. Bridgewater, NJ: Aventis; 2004 July.
6. CHEST. 2004; 126:S338-400.
7. CHEST. 2004; 126:S401-28.
8. Ann Intern Med. 1994; 121:81-9.
9. Clin Pharmacol Ther. 2005; 77:542-52.
10. Ther Drug Monit. 2004; 26:305-10.
11. J Clin Pharmacol. 2003; 43:586-90.
12. Obes Surg. 2002; 12:19-24.
13. Pharmacotherapy. 2001; 21:218-34.
14. Am Heart J. 2004; 148:582-9.
15. Am Heart J. 2002; 143:753-9.
16. Clin Pharmacol Ther. 2005; 77:542-52.
17. Pharmacotherapy. 2001; 21:169-74.
18. J Clin Pharmacol. 2003; 43:586-90.

PHARMACY AND THERAPEUTICS SUBCOMMITTEE ACTIONS

DRUGS ADDED TO STOCK

ANTIPYRINE AND BENZOCAINE

Otic Solution

This combination product (Auraglan®) is indicated for the management of pain associated with acute otitis media, as well as pain associated with foreign body injuries to the ear.

ANTITHROMBIN III

Injection

Antithrombin injection (Thrombate III® - Bayer) is indicated for the treatment of patients with hereditary antithrombin III deficiency in conjunction with surgical procedures or the management of thromboembolism.

Note: The prescribing of antithrombin III injection is restricted to Hematology attending physicians.

CEFTAZIDIME

Injection: 1 gm, 2 gm

Ceftazidime (Fortaz® - GSK) is a cephalosporin antibiotic. It is useful for the treatment of multi-resistant strains of *Pseudomonas aeruginosa*.

Note: The use of ceftazidime is restricted to the treatment of Pseudomonas infections.

COLLAGENASE

Topical Ointment: 250 units per gram

Collagenase (Santyl® - Ross) is an enzymatic debriding ointment.

DOXEPIN

Topical Cream: 5%

Doxepin topical cream (Prudoxin® - Doak) is indicated for the management of pruritus.

DULOXETINE

Delayed Release Capsules: 20 mg, 30 mg, 60 mg

Duloxetine (Cymbalta® - Lilly) is indicated for the treatment of major depressive disorder.

ERLOTINIB

Tablets: 150 mg

Erlotinib (Traceva® - OSI/Genentech) is indicated for the treatment of refractory locally advanced or metastatic non-small cell lung cancer.

DRUGS ADDED TO STOCK (CON'T)

FLUOCINOLONE ACETATE

Intravitreal Implant: 0.59 mg
Fluocinolone intravitreal implants (Retisert® - Bausch & Lomb) is indicated for the treatment of uveitis.

Note: The prescribing of Retisert® is restricted to Ophthalmology.

IBANDRONATE

Tablets: 150 mg
Ibandronate (Boniva® - Roche) 150 mg tablets are indicated for once monthly dosing for the treatment and prevention of osteoporosis.

OXANDROLONE

Tablets: 2.5 mg and 10 mg
Oxandrolone (Oxandrin® - Savient) is an anabolic steroid indicated as adjunctive therapy to promote weight gain.

Note: Protocol Drug; the prescribing of oxandrolone is restricted to patients treated in the Burn Unit. Orders must be signed by Burn Unit attending physicians.

PORFIMER

Injection: 75 mg
Porfimer (Photofrin® - Axcan Scandi Pharm) is a photosensitizing agent used in the photodynamic therapy of tumors.

SODIUM PHENYLACETATE AND SODIUM BENZOATE

Injection: 50 ml vial
This product (Ammonul® - Ucylyd) is indicated as adjunctive therapy for the treatment of hyperammonemia in patients with deficiencies of the urea cycle.

TIPRANAVIR

Capsules: 250 mg
Tipranavir (Aptivus® - BI) is a protease inhibitor indicated for the treatment of resistant strains of HIV-1 virus.

ZICONOTIDE

Injection: 25 mcg/ml, 100 mcg/ml
Ziconotide injection (Prialt® - Elan) is a neuronal calcium channel blocker indicated for the management of severe chronic pain in patients where intrathecal therapy is warranted and who are intolerant or refractory to other treatments.

Note: The prescribing of ziconotide injection is restricted to prescribing by the Pain Medicine Service.

DRUGS DELETED FROM STOCK

CARMINE RED CAPSULES

Discontinued due to low use.

CEFOTETAN INJECTION

Discontinued by the manufacturer. Alternative antibiotic therapy (e.g., cefazolin plus metronidazole) is available.

DRUGS DELETED FROM STOCK (CON'T)

DIHYDROTACHYSTEROL TABLETS AND ORAL SOLUTION

Discontinued by the manufacturer. Calcitriol is available.

HISTAMINE PHOSPHATE INJECTION

Discontinued due to low use.

HYDROMORPHONE SUSTAINED-RELEASE CAPSULES

(Palladone®)

Discontinued by the manufacturer due to safety concerns.

INSULIN HUMAN, ZINC SUSPENSION (Extended) (Ultralente)

(Humulin U®)

Discontinued by the manufacturer.

INSULIN HUMAN, ZINC SUSPENSION (Lente) (Humulin L®)

Discontinued by the manufacturer.

OBRITE® CONTACT LENS CLEANING SOLUTION

Discontinued by the manufacturer.

PROCHLORPERAZINE ORAL SOLUTION

Discontinued by the manufacturer. Prochlorperazine injection, tablets, and suppositories are available.

ADDITIONAL ACTIONS

DARBEPOETIN ALFA INJECTION (ARANESP®)

A 150 mg per 0.3 ml syringe has been added to stock.

ESTRADIOL TRANSDERMAL PATCH

The Vivelle® brand of estradiol transdermal patch has replaced the Esclim® brand, which was discontinued by the manufacturer. Orders written for Esclim® will be converted to an equivalent strength of Vivelle®.

FLUTICASONE ORAL INHALER

A 44 mcg per inhalation formulation (Flovent HFA® 44 mcg) was added to stock.

HYDROXYZINE 2 mg PER ml ORAL SOLUTION

This product has been added to stock; it is a replacement for hydroxyzine 5 mg per ml oral solution.

RIBAVIRIN

A 40 mg/ml oral solution was added to stock.

SUCROSE

A 24% oral solution has been added to stock.

TETANUS TOXOID-REDUCED DIPHTHERIA TOXOID-ACELLULAR PERTUSSIS VACCINE, ADSORBED (ADACEL®)

This vaccine known as "Tdap" is indicated as a single-dose booster vaccine for persons 11 through 64 years of age who have completed the primary vaccination series.

