Enoxaparin

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Abstract

The development of low-molecular and ultra-low-molecular weight heparins has changed anticoagulation treatment options. Enoxaparin is a low-molecular weight heparin (LMWH), which works on Factor Xa and is indicated for both the prevention and treatment of various thrombotic conditions. Dosing is individualised to patient and condition. There is uncertainty about the dose in obese patients, with no clear consensus on an appropriate dose. COVID-19-associated coagulopathy has resulted in the investigation of enoxaparin to help reduce mortality.

Keywords: enoxaparin, LMWHs, COVID-19, coagulopathy, Factor Xa

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Introduction

Unfractionated heparin (UFH) has had little competition as an anticoagulant for almost 50 years. It has maintained this status mainly because its anticoagulant effects are rapid and clinically effective.[1] However, the development of low-molecular and ultra-low-molecular weight heparins has changed the anticoagulant treatment landscape and drugs such as enoxaparin (Clexane®) have become popular.

Pharmacology

Enoxaparin is a low-molecular weight heparin (LMWH) with an average molecular weight of only 4–5 kD compared to UFH's 15 kD.[1,2] LMWHs are produced from UFH by depolymerisation. This changes the properties of LMWHs, leading to clinical advantages over UFH. The different methods of preparation result, to some degree, in differences in their pharmacokinetic properties and anticoagulant profiles – such that these drugs are not clinically interchangeable.[3]

Mechanism of action

LMWHs mainly act on coagulation Factor Xa, and to a lesser extent, on thrombin (Factor IIa). Enoxaparin binds to and potentiates antithrombin III which is a serine protease inhibitor resulting in a complex that irreversibly inactivates Factor Xa.[4] Enoxaparin has less activity against thrombin compared to UFH. Interestingly, the major mechanism of action of factor Xa inhibitors is reflected in their nomenclature. Hence eno***xa***parin.

Positioned at the junction of the intrinsic and extrinsic coagulation pathways, Factor Xa transforms prothrombin into thrombin.[4] The added thrombin activity of enoxaparin restricts the intensification of the coagulation cascade by thrombin (Figure 1).[4-6]

Indications for the use of enoxaparin

Enoxaparin's indications include acute coronary syndromes (ACS) such as ST-elevation myocardial infarction, non-ST elevation myocardial infarction, and unstable angina. The main aim in patients with ACS is to reduce and prevent the risk of further ischaemic events. Enoxaparin and other LMWHs have the added advantage of minimal laboratory monitoring. Furthermore, in several clinical trials (ESSENCE, TIMI 11B and ASSENT 3) LMWHs have proven to be superior in the management of unstable coronary syndromes.[7,8]

Other indications include deep vein thrombosis (DVT), which is particularly common after total hip surgery.[9]

LMWHs reduce the incidence of major bleeding during the initial treatment phase, as well as the overall mortality rate during the follow-up phase.[4] Enoxaparin is normally recommended at 1 mg per kg of body weight (Figure 2).[9]

Anticoagulants are the mainstay treatment for pulmonary embolisms (PE) that presents as shock, sustained hypotension, mild dyspnoea or may even be asymptomatic.[9]

Other indications include venous thromboembolism secondary to malignancy; primary prevention of venous thromboembolism (VTE); treatment for prosthetic valve thrombosis in pregnancy;

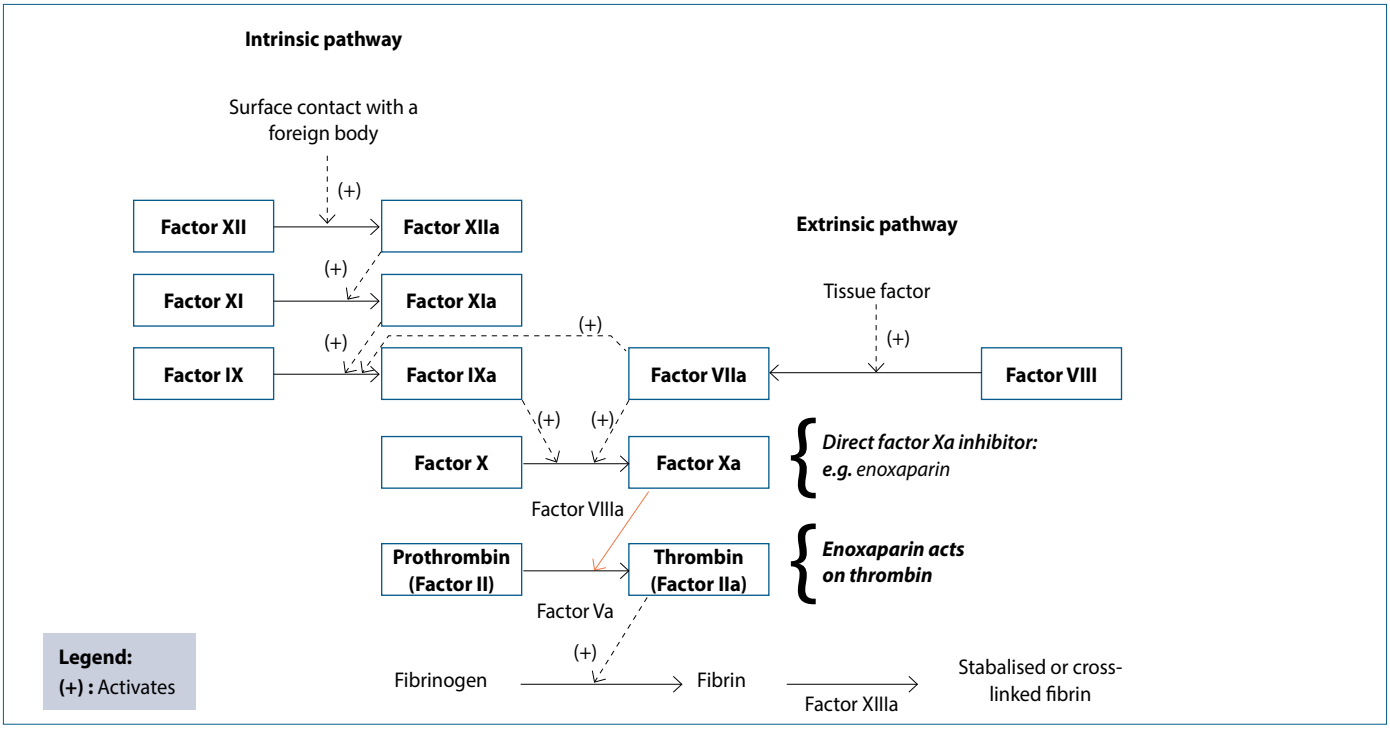


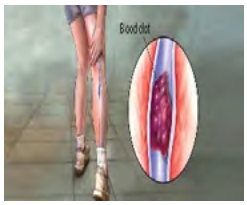
Figure 1: The clotting cascade and site of action of enoxaparin[4]

treatment for VT in pregnancy; antiphospholipid antibody syndrome; arterial thromboembolism prophylaxis; cerebral thromboembolism; percutaneous coronary intervention (PCI) and peri-procedural anticoagulation.[5,6]

Administration

Enoxaparin has a high bioavailability and reaches peak plasma activity within 3–5 hours,[6] with superior bioavailability and a longer half-life compared to UFH.[10-12] Further advantages of enoxaparin are listed in Table I. The drug is metabolised by the liver and eliminated renally, and therefore, dosage adjustments are required in renally impaired patients.[2]

Figure 2: Dosages of enoxaparin in prophylaxis or treatment[6]

	In the prevention of venous thrombosis after orthopaedic surgery: 40 mg once daily SC, initiated 12 hours preoperatively and continued for as long as risk persists
	Prevention of venous thrombosis in medical patients, SC, 40 mg once daily continued until fully ambulatory; minimum duration of therapy is 6 days Treatment of deep vein thrombosis, SC, 1 mg/kg lean body mass 12 hourly, usually for 5–10 days or until oral anticoagulation is established
	Unstable angina, SC, 1 mg/kg 12 hourly given concurrently with aspirin, minimum duration of therapy is 2 days
****Renal impairment**	Creatinine clearance < 30ml/min. Prevention SC, 20 mg once daily and treatment SC, 1 mg/kg once daily

Recommended dosage

Unless treatment is urgently required, all patients should be evaluated for a bleeding disorder prior to treatment initiation. Enoxaparin is a subcutaneous injection and can be given either prophylactically or as treatment, as outlined in Figure 2.[6]

Dosing of enoxaparin in obese patients

As of yet, there are no official dosing recommendations for the obese population; however, current data suggests that a reduced weight-based dose (less than 1 mg per kg) is prudent to achieve therapeutic peak anti-Xa levels.[9,10] Standard dosing of enoxaparin in morbidly obese patients will likely lead to supratherapeutic anti-Xa levels.[13-15]

Although there is no clear consensus, it is suggested that patients be dosed individually, based on their clinical presentation, with regular monitoring of anti-factor Xa levels to guide

Table I: Advantages of enoxaparin[2]

- Minimal plasma protein binding (better anticoagulant effects) – thus removing the need for therapeutic drug monitoring
- Better capacity to release tissue factor pathway inhibitor
- Higher anti-factor Xa:IIa ratio
- Lower likelihood to inhibit platelet aggregation
- Less inhibition of platelet factor IV
- Less likely to cause heparin-induced thrombocytopenia and osteoporosis

dose adjustments. There is a definite need for further investigation to improve appropriate dosing in this population.[16]

Drug interactions

Agents that may increase the risk of haemorrhage should be discontinued prior to the initiation of LMWH therapy. These include other anticoagulants and platelet inhibitors (including acetylsalicylic acid, salicylates, NSAIDs, dipyridamole or clopidogrel). Should co-administration be necessary, close clinical and laboratory monitoring is required. Other side-effects include nausea, confusion, headache, gastrointestinal bleeding, hypoaldosteronism, liver injury and rectal sheath haematoma.[5]

Contraindications

Severe uncontrolled hypertension, haemorrhagic cerebrovascular accident, an active gastric or duodenal ulcer or active major bleeding such as a GI bleed, haemophilia and a known hypersensitivity to enoxaparin are some of the contraindications to its use.[5]

COVID-19-associated coagulopathy

A clear association between COVID-19 and thromboembolisms has been establish, with numerous reported findings of coagulopathy, both venous and arterial, in patients with severe COVID-19. Despite these findings, the exact pathogenesis of COVID-19-induced coagulation remains unclear.[17-19]

COVID-19 causes a hypercoagulable state and despite anticoagulant therapy (heparin) in prophylactic dosages there is still a 31% incidence of venous as well as arterial thrombosis increasing to 49% in patients admitted to the intensive care units. Therefore, therapeutic dosages should be used. Helms et al. suggested titrating anticoagulant treatment to measured anti-FX activity and possibly aiming for higher levels.[16] In patients admitted to ICU with COVID-19 pneumonia, 27% of patients presented with DVTs and 81% developed pulmonary embolism.[20]

COVID-19 induces pro-inflammatory markers, a prothrombotic state and in severe cases a cytokine storm, causing release of microthrombi via coagulation cascade activation resulting in organ-restricted coagulopathy.[17-19]

COVID-19-associated coagulopathy positively correlates with a marked elevation of fibrin, fibrin degradation products, fibrinogen, D-dimer, decreased platelet counts, with a mild effect on prothrombin pime (PT) and partial thromboplastin time (PTT).[17-19]

Based on these findings, and reported cases of worse clinical outcomes in patients with elevated markers, it is proposed that anticoagulation therapy may play a key role in the management of COVID-19. Proper anticoagulation has a positive impact on survival.[17]

The latest guidelines recommend that all COVID-19 hospitalised patients, without contraindications to anticoagulation therapy, receive prophylactic treatment with LMWH.[19] In addition, the WHO recently published an updated clinical management of COVID-19 guideline, which includes the use of anti-thrombotic agents.[17,18]

The recommendation is that thromboprophylaxis doses of anti-coagulation be used, rather than intermediate or therapeutic dosing, if no established indication for higher dose of anticoagulation exists.[18]

It's important to note that the data are limited and that more studies are needed to evaluate the risk versus benefit of using LMWH in hospitalised COVID-19 patients.[19] Currently the weight of evidence suggests a possible reduction in mortality and pulmonary embolism.[18]

Recommendation for the use of enoxaparin in COVID-19

Enoxaparin is currently under investigation in severe COVID-19 hospitalised cases.[6,18]

It should be dosed according to thromboprophylaxis doses, until hospital discharge, as there is currently insufficient data to recommend either for or against using therapeutic doses.[17,18]

More information regarding specific dosing and population groups can be found inside the WHO's COVID-19 Clinical Management: Living Guidance published on the 25 January 2021, or for developing details, please visit the Coronavirus Disease 2019 (COVID-19) Investigational Therapies Drug Consults.[6]

Conclusion

Enoxaparin inhibits coagulation Factor Xa, and to a lesser extent thrombin, which ultimately limits the coagulation cascade. Dosage adjustments are required in patients with impaired renal function. Furthermore, in obese patients, dosing should be individualised, and the effects on anti-factor Xa levels monitored. A clear association between severe COVID-19 and thromboembolisms exists, and based on these findings, there is consensus regarding the use of enoxaprin thromboprophylaxis dosing to improve clinical outcomes.

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References

1. Fareed J, Hoppensteadt D, Walenga J, et al. Pharmacodynamic and pharmacokinetic properties of enoxaparin. Clinical Pharmacokinetics. 2003 Oct;42(12):1043-57. https://doi.org/10.2165/00003088-200342120-00003.
2. Carter NJ, McCormack PL, Plosker GL. Enoxaparin. Drugs. 2008;68:691-710. https://doi.org/10.2165/00003495-200868050-00012.
3. Fareed J, Ma Q, Florian M, et al. Unfractionated and low-molecular-weight heparins, basic mechanism of action and pharmacology. Seminars in Cardiothoracic and Vascular Anesthesia. 2003;7(4):357-77. https://doi.org/10.1177/108925320300700402.
4. Schellack G, Modau T, Schellack N. 2016. Clinical overview of venous thromboembolism. South African Family Practive. 2016;58(1):39-45.
5. Jupalli A, Iqbal AM. Enoxaparin. [Updated 15 Jul 2020]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK539865/.
6. Siddiqui MA, Wagstaff AJ. Enoxaparin. Drugs. 2005 May 1;65(7):1025-36. https://doi.org/10.2165/00003495-200565070-00009.
7. Budaj A, Eikelboom JW, Mehta SR, et al. Improving clinical outcomes by reducing bleed-

ing in patients with non-ST-elevation acute coronary syndromes. European Heart Journal. 2009 Mar 1;30(6):655-61. https://doi.org/10.1093/eurheartj/ehn358.
8. Bergqvist D, Benoni G, Björgell O, et al. Low-molecular-weight heparin (enoxaparin) as prophylaxis against venous thromboembolism after total hip replacement. New England Journal of Medicine. 1996 Sep 5;335(10):696-700. https://doi.org/10.1056/NEJM199609053351002.
9. Agnelli G, Becattini C. Acute pulmonary embolism. New England Journal of Medicine. 2010 Jul 15;363(3):266-74. https://doi.org/10.1056/NEJMra0907731.
10. Ibbotson T, Goa KL. Enoxaparin. Drugs. 2002 Jun;62(9):1407-31. https://doi.org/10.2165/00003495-200262090-00017.
11. Noble S, Peters DH, Goa KL. Enoxaparin. Drugs. 1995 Mar;49(3):388-410. https://doi.org/10.2165/00003495-199549030-00006.
12. Buckley MM, Sorkin EM. Enoxaparin. Drugs. 1992 Sep 1;44(3):465-97. https://doi.org/10.2165/00003495-199244030-00010.
13. Gibbs L, Sheley J. Rreatment of venous thromboembolism in patients who are morbidly obese. Am Fam Physician. 2018 Apr 15;97(8):497-98.
14. Thompson-Moore NR, Wanat MA, Putney DR, et al. Evaluation and pharmacokinetics of treatment dose enoxaparin in hospitalised patients with morbid obesity. Clinical and Applied Thrombosis/Hemostasis. 2015;21(6):513-20. https://doi.org/10.1177%2F1076029614568713.
15. Lee YR, Palmere PJ, Burton CE, Benavides TM. Stratifying therapeutic enoxaparin dose in morbidly obese patients by BMI class: a retrospective cohort study. Clinical Drug Investigation. 2020;40(1):33-40. https://doi.org/10.1007/s40261-019-00855-9.
16. Barras M, Legg A. Drug dosing in obese adults. Aust Prescr. 2017;40:189-93. https://doi.org/10.18773/austprescr.2017.053.
17. Hadid T, Kafri Z, Al-Katib A. Coagulation and anticoagulation in COVID-19. Blood Revies. 2020;100761. https://doi.org/10.1016/j.blre.2020.100761.
18. Who.int. 2021. COVID-19 clinical management: living guidance. [Internet] Available from: https://www.who.int/publications/i/item/WHO-2019-nCoVclinical-2021-1. Accessed 8 Feb 2021.
19. Karimzadeh S, Dong V, Hassan O, et al. Covid-19-induced coagulopathy and observed benefits with anticoagulation. Transfus Apher Sci. 2020;59(6):102906. https://doi.org//10.1016%2Fj.transci.2020.102906.
20. Helms J, Tacquard C, Severac F, et al. 2020. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med. 2020;46(6):1089-98. https://doi.org/10.1007/s00134-020-06062-x.