Canterbury District Health Board
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Clinical Pharmacology Bulletin

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Low Molecular Weight Heparin (LMWH) - How to dose

LMWH is increasingly used for treatment of venous thromboembolic disease (VTE), acute coronary syndrome (ACS) and in medical and surgical VTE prophylaxis. Certain patient groups are at high risk of adverse events if the dose of LMWH is not adjusted appropriately. This bulletin aims to improve safe prescribing of LMWH.

Mechanism of Action

LMWH works largely through its anti-factor Xa activity (approximately 100 IU/mg). Factor X plays a central role in thrombin generation, based on its position at the start of the final common coagulation pathway. Interference with factor Xa activity reduces the amount of active thrombin generated and, therefore, the amount of fibrin formed.

Dosing of LMWH

In CDHB, 95% of LMWH used is enoxaparin, but the same principles apply to dalteparin and tinzaparin.

- **In patients with normal renal function:**

(i) VTE prophylaxis: Enoxaparin 20-40mg daily.
(ii) VTE or ACS treatment: Enoxaparin either 1.5mg/kg once daily or 1mg/kg twice daily.

- **In patients with impaired renal function**:

(i) VTE prophylaxis: Enoxaparin 20mg (low risk surgery) or 40mg (high risk surgical & medical patients) daily. The dose should be reduced if CrCL ≤60 mL/min.
(ii) VTE or ACS treatment: The first dose of LMWH should be calculated using actual bodyweight. Subsequent doses must be adjusted for renal function because 70% of the dose of LMWH is excreted unchanged through the kidneys (f_u=0.7). Unless the dose is reduced in renal impairment, prolonged and excessive anti-Xa activity will occur, increasing the risk of haemorrhage.To calculate the maintenance dose of LMWH in renal impairment:

1. Calculate the patient's creatinine clearance, using either the Cockcroft & Gault formula or the eGFR supplied by the laboratory (based on the MDRD formula).
2. Use the formula from page 162 of the Pink Book to calculate the renally-adjusted dose rate (DR) for your patient.

$$DR(patient) = \left[(1 - fu) + fu\left[\frac{\text{Calculated CrCL(mL/min)}}{100(\text{mL/min})}\right]\right] \times DR\ (normal)$$

In patients with a CrCL ≤30ml/min, it is safer to use unfractionated heparin (UFH), which can be quickly reversed by protamine. If LMWH is used in such patients, monitoring of anti-Xa activity is recommended. Discuss with haematology.

LMWH dosing in obesity

Actual body weight should be used to calculate the treatment dose of LMWH. However safety data in patients over 150kg is lacking, and factor Xa monitoring is recommended. The maximum dose of dalteparin is 18,000u/day.[1]

Contra-indications and Cautions

- Active or history of peptic ulcer disease
- Any bleeding diathesis
- Uncontrolled severe hypertension
- Recent neuro-ophthalmologic injury or surgery, including previous intracerebral haemorrhage

The risks of LMWH

1) Haemorrhage

LMWH causing fatal haemorrhage in patients is not uncommon. In most of these cases, the patient was on an inappropriately high dose of LMWH, and/or was prescribed other drugs that interfere with haemostasis.
The risk of haemorrhage is increased with:
(i) increasing age; (ii) female sex; (iii) low body weight;
(iv) reduced creatinine clearance; (v) number of enoxaparin doses received; (vi) concurrent aspirin, clopidogrel, warfarin or NSAIDs; (vii) previous peptic ulcer disease. [2]
A large clinical trial showed that 1.2% of patients with normal renal function developed major bleeding with LMWH, compared with 2% of patients with moderate renal impairment (CrCL 30-60ml/min) and 6% of patients with severe renal impairment (CrCL ≤ 30ml/min) whose dose of LMWH was not adjusted for their renal impairment.

2) Heparin-induced Thrombocytopenia (HIT)

HIT is defined as a platelet drop of ≥ 50% and the presence of the HIT antibodies. HIT is more common with UFH (about 2.5%) than LMWH therapy (about 0.5%). It usually occurs with heparin courses of longer than 5 days, and should be suspected when a patient on heparin develops a new venous or arterial thrombosis.
Mild, transient, asymptomatic thrombocytopenia has been reported during the first days of therapy which is usually self-limiting, and does not imply development of HIT. HIT is caused by development of antibodies to the heparin/platelet-factor 4 complex. This results in platelet activation which can cause venous and arterial thromboses. Check the platelet count prior to starting LMWH, then every three to five days while on LMWH. If the platelet count drops by ≥50%, stop LMWH and contact haematology. [3]

Factor Xa Monitoring

Patients who are at extremes of weight (<45 kg or >150kg), as well as patients with severely impaired renal function (CrCL ≤30ml/min) should be monitored by factor Xa assay. Discuss with haematology.

Reversal of LMWH

Protamine 1mg, by slow intravenous infusion, neutralises the anticoagulant effect of 1mg of enoxaparin if administered within 8 hours. Reversal of LMWH by protamine is slower and may not be complete. For this reason the use of UFH may be safer in patients with a high risk of haemorrhage.

References

1) Yee J, Duffull S. The effect of weight on dalteparin pharmacokinetics. A preliminary study. Eur J Clin Pharmacol 2000 Jul;56(4):293-7
2) Macie C, Forbes L, Foster G et al. Dosing Practices and Risk Factors for Bleeding in Patients Receiving Enoxaparin for the Treatment of an Acute Coronary Syndrome* Chest. 2004;125:1616-1621
2) Prandoni P, Siragusa S, Girolami B .The incidence of heparin-induced thrombocytopenia in medical patients treated with low molecular weight heparin. Blood 2005, Nov; 106(9):2931- 32