WeMeReC
Welsh Medicines Resource Centre
Canolfan Adnoddau Moddion Cymru

Bulletin

"Independent prescribing information for NHS Wales"

Using low molecular weight heparin:

incorporating advice from the All Wales Medicines Strategy Group

Low molecular weight heparins (LMWHs) are fragments of naturally occurring unfractionated heparin (UFH), which have largely replaced the use of UFH in the routine treatment and prophylaxis of venous thromboembolism (VTE). LMWH requires less monitoring than UFH and may be self-administered subcutaneously once or twice daily. This has led to concerns being raised about an increased volume of prescribing in primary care and a lack of information and guidance to support prescribers.

This bulletin looks at the appropriate prescribing and monitoring of LMWH for the treatment and prophylaxis of VTE in adults. The use of LMWH for other indications, such as haemodialysis and acute coronary syndrome, is not covered. Where the All Wales Medicines Strategy Group (AWMSG) has made a **Recommendation** for the use of LMWH, it appears in **bold** text. Where a *Good Practice Point* has been highlighted by the AWMSG, it appears in *italics*.

Product differences

The LMWHs that are currently available in the UK are bemiparin (*Zibor*®▼), dalteparin (*Fragmin*®▼), enoxaparin (*Clexane*®), and tinzaparin (*Innohep*®). These products have biologically similar actions but are chemically different, with a range of molecular weights.[1] Licensed indications also vary and the products are not necessarily interchangeable in practice.

All LMWHs exert their anticoagulant effect primarily through the inactivation of factor Xa (anti-Xa activity) but the different preparations also have varying anti-IIa activity. It is probable that both actions contribute to the antithrombotic effects of the medicines, but where monitoring of effect is necessary (see page 2), anti-Xa activity is the only measurement that can be used.[1] A full discussion of the properties and adverse effects of LMWHs and how they compare with UFH can be found in the WeMeReC bulletin on LMWH (June 2007) at www.wemerec.org.

Summary

- The different LMWHs are similar but not necessarily interchangeable.
- When determining the dose required, indication and renal function need to be considered. Where a weight calculation is also required, this must be accurate, acted upon, and noted in the patient record.
- Platelet counts should be monitored in patients at increased risk of developing heparin-induced thrombocytopenia (see page 2).
- Routine monitoring of the activity of LMWH is unnecessary. Where such monitoring is required, anti-Xa assay should be used (see page 2).
- Serum electrolytes should be monitored in patients at risk of developing hyperkalaemia (see page 2).
- While hospital use of LMWH is extensive, prescribing in primary care is restricted to shared-care use in limited circumstances (see pages 2-4).
- Monitoring and the appropriate use of shared-care protocols are vital for the safe use of LMWH.
- Patient buy-in, education, and follow-up are important to increase concordance and decrease waste.

Dosing considerations

When deciding on the preparation to be used and the dose to administer, prescribers should consider the following for each patient episode:

- **Patient risk** – the intrinsic risk of thrombosis or bleeding, i.e. the haemostatic potential.
- **Disorder risk** – the risk of thrombosis or bleeding associated with the disorder or procedure.
- **Heparin risk** – the relative efficacy and bleeding risk associated with the preparation.[1]

The National Patient Safety Agency and NHS Litigation Authority have reported cases of severe harm and deaths with the use of LMWH.[2] Given the relatively long half-life of elimination of LMWH and the fact that the anticoagulant action is difficult to reverse (protamine sulphate is only partially effective), it is imperative that doses are determined accurately. Weight and renal function should be taken into account where appropriate.

Welsh Medicines Resource Centre
Academic Centre, University Hospital Llandough,
Penarth, Vale of Glamorgan CF64 2XX

Tel: 029 2071 6117 Web: www.wemerec.org
Email: wemerec@wales.nhs.uk

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Weight

When used for the prophylaxis of VTE, LMWH is administered as a standard dose based on the indication and risk stratification of the patient. A specific exception to this is where tinzaparin is used for prophylaxis in orthopaedic surgery: in this case dose is determined by weight. When treatment doses are given for any indication, the patient's weight always needs to be taken into account.[3]

Dosing errors have occurred when patients have not been accurately weighed. Where a patient's weight is required it must be recorded accurately in kilograms. This should be determined using reliable weighing equipment and not by estimation or self-reporting. Patients should be weighed at the start of therapy and, if necessary, during treatment.[2]

Because LMWH distributes poorly into fatty tissue, it is possible that obese patients may receive supra-therapeutic doses if calculations are based on total body mass alone.[4,5] However, obese patients are at higher risk of VTE and illogical dose reduction may lead to treatment failure.[4] Using the recommended weight-adjusted dose is not thought to significantly increase bleeding or VTE risk.[4,5] However, specialist advice may be necessary for the very obese, particularly those undergoing high risk procedures such as bariatric surgery.

Renal function

Patients with renal impairment are at increased risk of LMWH accumulation and require careful assessment and subsequent observation for signs and symptoms of bleeding. Renal function, based on estimated creatinine clearance or estimated glomerular filtration rate (eGFR), needs to be taken into account when determining the dose.[2,3] The extent to which different LMWHs are reliant on renal excretion varies;[4] the manufacturers of some products specify a lower dose in renal failure and/or suggest that consideration is given to the use of UFH instead (as UFH is handled mainly via the liver).[3] Renal impairment combined with other risks, especially in the frail or very elderly, may preclude use.

Monitoring

Platelet count

Heparin-induced thrombocytopenia (HIT) is a rare but potentially life-threatening adverse effect that leads to a hypercoagulable state.[6] HIT usually occurs between days five and 21 of treatment. The prevalence is lower with LMWH than with UFH.[7]

All patients who receive heparin should have their platelet count measured on the day of initiation. (Any patients who have received any heparin within the previous 100 days should have another measurement taken after 24 hours.[7]) For all surgical and medical patients receiving LMWH, and obstetric patients receiving treatment doses, further platelet counts should be carried out every two to four days from days four to 14.[7] 'Regular' monitoring beyond this is not defined and monitoring in clinical trials has varied widely; guidance from the initiating specialist may be necessary. A monthly interval has been proposed as suitable for cancer patients in shared care.[8] Obstetric patients receiving prophylaxis are considered to be at low risk and do not require routine monitoring.[7]

Where the platelet count falls by 50% or more, or to below the normal range, and/or the patient develops new thrombosis or skin allergy in this time, HIT should be suspected and a clinical assessment made.[7] If the probability of HIT is high, LMWH should be stopped and specialist advice sought urgently.

Anti-Xa activity

Routine monitoring of the anti-Xa activity of LMWH is not required. Measurement of activity may be of value where the standard or weight-adjusted dose of LMWH is likely to be unreliable and the patients are therefore at a higher risk of bleeding or thrombosis,[1] e.g. in patients with severe renal failure, in pregnancy, and in patients at the extremes of body weight. Some manufacturers recommend monitoring of the elderly in certain circumstances, but age alone is not an indication for this.

Target values for anti-Xa activity vary by LMWH type and are not well established. When used to guide therapy, measurements should normally be taken around four to six hours after the last dose to determine peak effect.[1,5,6]

Where there is a need to monitor treatment by measuring the anti-Xa level, LMWH should be prescribed and use followed up regularly by specialist services.[8]

Serum electrolytes

The effect of aldosterone is reduced by LMWH and this may result in hyperkalaemia. Symptomatic hyperkalaemia is unlikely unless there is a concurrent cause.[1] The risk appears to increase with duration of use. Serum electrolytes should be monitored in at-risk patients, including those with diabetes mellitus; chronic renal failure; pre-existing metabolic acidosis; elevated plasma potassium; or those taking potassium-sparing medicines or potassium supplements.

Prophylaxis of VTE in hospitalised patients

All patients should be assessed for risk of VTE on admission to hospital. Appropriate anticoagulation should be provided to those at increased risk; in some patients this will be LMWH. The risks of bleeding and VTE should be re-assessed within 24 hours of admission and with changes in clinical status.[9]

Medical patients are regarded as being at increased risk of VTE if they have or are expected to have significantly reduced mobility for at least three days, or relatively decreased mobility and one or more of the risk factors in Box 1.[9]

Surgical patients are at increased risk of VTE if one or more risk factor/s (see Box 1) is/are present or if: significant immobility is expected; anaesthetic time is greater than 90 minutes (60 minutes for surgery of the pelvis or lower limb); they required admission with inflammation or an abdominal condition.[9]

Box 1. Risk factors for VTE[9]

- Active cancer or cancer treatment (see page 4)
- Age > 60 years
- Critical care admission
- Dehydration
- Thrombophilias, e.g. antiphospholipid syndrome, protein C or S deficiency, antithrombin deficiency
- Obesity (BMI > 30 kg/m^2)
- One or more significant co-morbidities including: heart disease; metabolic, endocrine, or respiratory pathologies; acute infection; inflammatory disease
- History of VTE – personal or in a first-degree relative
- Use of HRT or oestrogen-containing contraceptive
- Varicose veins with phlebitis
- Pregnancy (see discussion below)

The recommended duration of prophylaxis varies by site and type of surgery. For example, in orthopaedic patients, duration ranges from 10-14 days for knee surgery to 28-35 days for hip surgery.[9]

LMWH treatment, for any indication, for four weeks or less should be prescribed and monitored by the initiating physician.[8]

If patients are discharged with prophylactic LMWH, part of the discharge plan should include written and verbal information regarding the correct duration of use, the importance of continued correct use, signs of adverse effects, and the importance of seeking appropriate help in the case of problems arising.[9]

Perioperative advice should be provided by the hospital. If LMWH is advised, responsibility for prescribing, advising the patient, and informing the GP should normally be undertaken by the hospital.[10]

Treatment of VTE

The treatment of VTE is similar regardless of whether the patient presents with deep vein thrombosis (DVT) or pulmonary embolism. LMWH is typically used as the agent of choice to establish anticoagulation until oral therapy, e.g. warfarin, is optimised.[1] LMWH treatment is recommended for at least five or six days, depending on the agent, and is then withdrawn provided the INR has been within 0.5 units of target for two consecutive days.

In some circumstances LMWH can be used while awaiting the results of investigation in suspected DVT. The appropriateness of prescribing for this indication requires further consultation[10] and is currently determined locally.

Use in pregnancy and postpartum

The occurrence of a VTE is up to ten times more likely in pregnant than non-pregnant women of the same age and is the main direct cause of maternal death in the UK.[11] All women should undergo a documented assessment of risk factors for VTE before, or in early pregnancy. This should be repeated if admission to hospital is required or at the onset of other intercurrent problems.[12] Additional risk factors in pregnancy and the puerperium are shown in Box 2.

Box 2. Additional risk factors in pregnancy [8,12]

- Age > 35 years
- Pregnancy-related risk factor such as: ovarian hyperstimulation; multiple pregnancy; hyperemesis gravidarum; pre-eclampsia
- Excess blood loss or blood transfusion
- Caesarean section

Using LMWH in pregnancy may be difficult because of changes in weight as the pregnancy proceeds and differing bleeding risks for the mother and foetus.[5] No LMWH is currently licensed for use in obstetric practice but, with a substantial body of supporting evidence, such 'off-label' use has increased. LMWH is now considered the agent of choice for antenatal thromboprophylaxis as it is at least as effective as UFH and is considered to be safer.[1,2] Where dose is to be determined by weight, pre-pregnancy or booking weight should be used.

Guidance on the use of LMWH for prophylaxis and treatment of VTE in pregnancy and the puerperium has been produced by NICE[9] and the Royal College of Obstetricians and Gynaecologists.[11,12]

The prescribing of LMWH for the treatment of VTE in pregnancy should be 'hospital only'. Prescribing for the prophylaxis of VTE in pregnancy should normally be in secondary care.[8]

No recommendations can be made for prophylaxis in pregnant women where the decisive risk factor is obesity until 'standard practice' is agreed nationally.

It is essential that all women with a high risk of VTE receive preconception counselling, via specialist referral, at an early stage.

LMWH does not need to be initiated before pregnancy is confirmed, but should replace long-term warfarin by week six.[10] *Prophylactic LMWH can be used postpartum in adequately assessed patients until warfarin therapy is effectively re-established.*

Use in cancer

Active cancer and cancer treatment are themselves risk factors for VTE, both causing a hypercoagulable or prothrombotic state. Some degree of activation of the coagulation cascade, often complicated by medication and supportive measures, occurs in virtually all patients with active malignancy. This is thought to cause significant morbidity and mortality in cancer patients.[13]

Treatment of VTE with LMWH in cancer patients (i.e. patients undergoing cancer therapy or those who have metastatic disease) is suitable for shared care for up to six months.[8]

In this context, a straightforward shared-care arrangement would involve a GP prescribing LMWH, which was initiated for a patient by a specialist. Implicit in the arrangement is the fact that there continues to be specialist follow-up of the patient, with a clear plan and a defined protocol in place. This should include arrangements for monitoring as well as the responsibilities of the specialist, the GP, and the patient.[14] A shared-care protocol used in Wales for LMWH for the extended treatment or prophylaxis of VTE in patients with solid tumours is available via www.wales.nhs.uk/sites3/home.cfm?orgid=814.

Shared care should be agreed in writing with an invitation to participate from the consultant and a response from the GP.[8]

It is estimated that 1-2% of patients in general practice take warfarin, and that half of these do so for thromboprophylaxis of atrial fibrillation (AF).[10] If such a patient subsequently develops cancer, the risk of VTE and bleeding changes and there is currently a lack of clarity on the safest choice of anticoagulant. The risk-benefit ratio for anticoagulation should be formally re-assessed for the individual patient; a tool such as the $CHADS_2$ may be used to assess the risk of stroke.[10] (See WeMeReC bulletin on AF, May 2010.)

If uncertainty persists after considering the balance of risks and benefits, then the advice of a cardiologist or stroke physician should be sought.[10]

'Off-label' use

There are some circumstances where LMWH might be used off-label (i.e. outside the terms of its marketing authorisation). Such use in pregnancy has been described, but other examples might include circumstances where LMWH is used because warfarin is contraindicated or not tolerated. Informed consent for off-label use should always be obtained and documented.[9]

Off-label use of LMWH requires specialist advice.[10] *Prescribing responsibility for such use should be made on a case-by-case basis.*

Sub-therapeutic INRs

Prescribing LMWH for a low INR during warfarin therapy is only necessary in a small cohort of high-risk patients, e.g. those with recurrent VTE, or mechanical heart valves (if recommended by the cardiac surgeon).[10]

Patients on warfarin who are at high risk of VTE should be prescribed LMWH, by the department responsible for dosing warfarin, if the INR becomes sub-therapeutic.[10]

The patient partnership

Between a third and a half of medicines prescribed for extended periods are not used as prescribed, often due to a failure to properly agree the treatment with the patient and a lack of support thereafter.[15]

It is essential that patients understand the rationale for anticoagulation therapy, how to safely self-administer LMWH, and dispose of the sharps.

Prescribers should ensure that the prescription duration is appropriate for the indication, according to local or national guidelines.

Prescribers should consider establishing a register and recall system for patients using LMWH.[10]

The Summaries of Product Characteristics should be consulted for full prescribing information.

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