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Canolfan Adnoddau Moddion Cymru

Bulletin

"Independent prescribing information for NHS Wales"

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Low molecular weight heparin

Low molecular weight heparin (LMWH) has effectively replaced the routine use of unfractionated heparin (UFH) in the majority of patients. This bulletin discusses the use of LMWH for: the treatment of venous thromboembolism (VTE); the prophylaxis of VTE in surgical and medical patients; use in obstetric patients; and the treatment of acute coronary syndrome. The use of LMWH for other purposes, including haemodialysis is not covered.

LMWH products are fragments of standard or naturally-occurring UFH. They are produced by either chemical or enzymatic depolymerisation of the mucopolysaccharide heparin molecules. This process produces products with different pharmacodynamic and pharmacokinetic profiles.

There are a number of LMWH products available: bemiparin (*Zibor*®)▼, dalteparin (*Fragmin*®), enoxaparin (*Clexane*®), and tinzaparin (*Innohep*®). Despite few comparisons, current evidence suggests that the LMWH products are clinically similar, but not necessarily interchangeable.[1]

Comparative properties

UFH exerts its action by inhibiting clotting factor Xa and factor IIa (thrombin). Because of its smaller molecular size, LMWH has a greater effect on factor Xa than factor IIa (the ratio of activity varies depending on the individual LMWH product).[2] LWMH also has some antithrombin III-independent effects and, unlike UFH, does not bind extensively to platelets.

UFH is variably bioavailable after subcutaneous (SC) injection, highly bound to a variety of plasma proteins, and partly metabolised by the liver, all of which lead to wide inter- and intra-patient variability in response. In patients on UFH, activated partial thromboplastin time (aPTT) should be monitored and the dose adjusted to maintain an aPTT 1.5 - 2.5 times the control value. The kaolin cephalin clotting time (KCCT) is a widely used derivative of the aPTT.

Summary

- LMWH is commonly used for the treatment and prevention of venous thromboembolism and the treatment of acute coronary syndrome.
- LMWH is at least as safe and effective as UFH and has a number of advantages:
  - a more reliable relationship between doses and response
  - a longer plasma half-life allowing subcutaneous injection once or twice daily
  - no requirement for routine monitoring of response and dose adjustment
  - a reduced incidence of thrombocytopenia
  - a reduced incidence of osteoporosis
  - possible self-administration by patients.
- While routine monitoring of LMWH activity is not required, it might be considered in patients receiving treatment doses who are at increased risk of bleeding, such as: patients with renal impairment, those who are under or overweight, and women who are pregnant.
- Routine platelet counts are required before starting and during the first two weeks of LMWH therapy in most patients.

LMWH binds to plasma proteins to a lesser extent and is more predictably absorbed; it has a more predictable dose response and longer plasma half-life (four to five hours *vs* one hour). Thus, LWMH can be administered by SC injection once or twice daily, without the need for monitoring or dose adjustment in the majority of patients.

Where monitoring is desirable, anti-Xa assays should be used, because the aPTT is not significantly affected by LMWH. An anti-Xa assay may provide some guidance for dosing, but it should be recognised as a relatively poor predictor of bleeding or thrombosis risk.[1]

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

Tel: 029 2071 6117 Fax: 029 2071 5603
Email: wemerec@cardiffandvale.wales.nhs.uk

Treatment of venous thromboembolism

The treatment of VTE is similar whether presenting as pulmonary embolism (PE) or deep vein thrombosis (DVT). Trials comparing LMWH with UFH have shown that LMWH is at least as effective as UFH.[3] An improved safety profile (discussed in more detail on pages 3 - 4) and the lack of need for aPTT monitoring and dose adjustment has made LMWH the agent of choice for the initial treatment of VTE in patients who are suitable for anticoagulation.[1] Using LMWH helps to ensure adequate anticoagulation in the first few days of therapy when the effect of an oral agent is still not optimal, and thus reduce the risk of further complications.

Treatment with LMWH consists of once-daily SC injections of a weight-adjusted dose for at least five days until adequate oral anticoagulation is established for longer-term use. LMWH must be continued until the international normalised ratio (INR) has been within 0.5 units of target (e.g. 2.5) for at least two consecutive days. (In some settings, LMWH is also used in patients at high risk of VTE when the INR is sub-therapeutic and the oral anticoagulant dose is being adjusted.)

There is evidence to support the use of LMWH for outpatient management of DVT[4,5] and many hospitals now run outpatient DVT services. There is some evidence that PE can also be treated effectively in the outpatient setting.[6] Patients who may need to be more carefully assessed for outpatient treatment include those with thrombophilia, those with significant co-morbid illnesses, and those who may have difficulty coping with the administration requirements.

Prophylaxis of venous thromboembolism

Surgical patients

Virchow's triad of risk factors for thrombus formation (abnormalities of blood flow, of clotting components, and of the surfaces in contact with blood) are often present in immobile inpatients and surgical patients, especially those undergoing orthopaedic and lengthy operations. DVT occurs in about 30% of surgical patients (in over 40% of those undergoing major orthopaedic surgery) and is commonly asymptomatic.[7] The condition can lead to PE and sudden death. Symptomatic PE is reported in approximately 3% of surgical patients.[7] DVT can also lead to long-term problems with venous ulceration and post-thrombotic syndrome.

All hospital inpatients should be assessed for VTE risk and receive appropriate thromboprophylaxis.[8] Recent guidance from the National Institute for Health and Clinical Excellence (NICE), for inpatients undergoing surgery, lists patient-related factors that should be considered when assessing an individual's risk of thrombosis (Table 1)[7].

Table 1: Risk factors for VTE

- a history of VTE
- acquired or inherited thrombophilia
- cancer or cancer treatment
- use of combined oral contraceptives or hormone replacement therapy
- varicose veins with associated phlebitis
- obesity
- immobility
- prolonged travel before or after surgery
- age over 60
- acute medical illness
- severe infection
- heart or respiratory failure
- recent myocardial infarction (MI) or stroke
- inflammatory bowel disease
- nephrotic syndrome
- pregnancy or puerperium

The NICE guideline[7] contains a complete list of risk factors.

Preventative measures for patients undergoing surgical procedures include both mechanical and pharmaceutical prophylaxis. Most surgical patients will require thromboprophylaxis with a LMWH, UFH, or fondaparinux (see page 4), in combination with mechanical measures (e.g. graduated compression stockings).[1,7] LMWH has been shown to be as safe as UFH with some potential advantages in efficacy.[9] LMWH is typically administered once daily in fixed doses for prophylaxis of thrombosis.

Patients who have had major orthopaedic surgery are often discharged from hospital after four to five days but the risk of VTE may persist beyond this time. The optimum duration of anticoagulation is uncertain, but current guidelines suggest that these patients should be considered for LMWH (or fondaparinux) at recommended prophylactic doses for at least 7 to 10 days.[1] NICE recommends that patients having hip replacement surgery who have one or more individual risk factors and patients having surgery for hip fracture should have prophylaxis with LMWH or fondaparinux continued for four weeks after surgery.[7]

Medical patients

Many medical patients are at high risk of VTE (see Table 1 for individual risk factors); most PE-related hospital deaths occur in non-surgical patients.[1,8] Many hospital policies for prevention of VTE include recommendations for medical patients; however there is less clinical trial evidence in medical patients, and there are fewer validated tools for individual assessment.[1] Although there is no proven antithrombotic advantage for using LMWH over UFH, LMWH is often preferred for the reasons discussed previously.[1,10] There is some evidence that LMWH may be more effective than oral anticoagulants in patients with malignancy.[1]

Use during pregnancy

Pregnancy predisposes women to VTE, partly due to a change in the balance between clotting components in the blood. Additional risk factors for VTE during pregnancy include thrombophilia, previous VTE, obesity, and age over 35.[11]

None of the LMWH products are licensed for use during pregnancy; however LMWH, like UFH, is not known to cross the human placenta and, unlike warfarin, does not appear to be associated with any risk of teratogenesis or foetal haemorrhage.[12]

LMWH is increasingly being used in obstetric practice, since the available data (relating to use of enoxaparin, dalteparin and tinzaparin) suggest that it offers a safe and effective alternative to UFH.[1] The Royal College of Obstetricians and Gynaecologists (RCOG) has produced guidance on thromboprophylaxis during pregnancy[11] and on treating thromboembolic disease in pregnancy and the puerperium.[13] It is recommended that all women are assessed for VTE risk factors early in pregnancy or, where possible, before pregnancy. If problems develop or the patient is admitted to hospital, the risk assessment should be repeated.

Where thromboprophylaxis is necessary, doses of LMWH will be determined by the patient's early pregnancy body weight and on their level of risk.[11] There is generally no requirement for monitoring of response unless higher (twice daily) doses are being used or there are additional confounding factors. For the treatment of VTE, a twice daily LMWH regimen is recommended as elimination occurs more rapidly in pregnancy. Anti-Xa activity should be measured and the dose adjusted where necessary. The use of anticoagulant therapy during labour and delivery is discussed in the RCOG guidelines.

Management of acute coronary syndrome

Acute coronary syndrome (ACS) is the term generally used to encompass non-ST elevation MI or non-Q wave MI, and unstable angina. Studies have shown that in addition to the beneficial effects of aspirin, UFH reduces the risk of MI or death in patients with unstable angina.[14] LMWH is now widely replacing UFH. A meta-analysis comparing LMWH with UFH for ACS concluded that it had a similar effect on the risk of mortality, recurrent angina, and major or minor bleeding, but that LMWH was associated with a lower risk of MI, fewer revascularisation procedures, and fewer cases of thrombocytopenia.[15]

Enoxaparin and dalteparin are the only agents licensed for the treatment of ACS. Both are given as weight-adjusted, twice-daily, SC injections for two to eight days.

Safety of LMWH

Adverse effects reported with LMWH include:

- bleeding
- thrombocytopenia
- injection site reactions e.g. pain, haematoma, local irritation
- inflammatory nodules
- allergic reactions
- osteoporosis
- hyperkalaemia
- raised liver function tests.

Long-term use of heparin can cause **osteoporosis**: it decreases the number of osteoblasts, which reduces bone formation, and it increases the activity of osteoclasts, which increases bone resorption. Heparin-induced osteoporosis is slowly reversible. There is evidence that although osteoporosis can occur with LMWH, it occurs less frequently than with UFH.[1] LMWH is, therefore, often preferred where long-term use is predicted.

Heparin-induced **thrombocytopenia** (HIT) is a rare but serious adverse effect of therapy. It is caused by the development of an Ig G antibody to heparin-platelet factor 4 complexes. The incidence of HIT has been reported to be lower with LMWH, due to reduced binding with platelet factor 4.[1] All patients who are to receive heparin should have a platelet count on the day of starting treatment.[16] For surgical and medical patients receiving LMWH, and obstetric patients receiving treatment doses of LMWH, platelet counts should be measured every two to four days from days 4 to 14.

Other patients are at lower risk and do not require routine monitoring. If the platelet count falls by 50% or more, or falls below the normal reference range, and/or a patient develops new thrombosis or skin allergy between days 4 and 14 of treatment, the possibility of HIT should be considered, the heparin stopped immediately, and specialist advice sought; an alternative agent may be considered (e.g. danaparoid or lepirudin). HIT rarely develops beyond 14 days of treatment.

Managing bleeding and high-risk patients

Compared with UFH, the anticoagulant effect of LMWH persists for longer and is only partially reversed by protamine. UFH may be preferred in patients at high risk of bleeding, in whom rapid reversal of anticoagulation may be required.

Use in patients with renal impairment

LMWH is excreted predominantly via the kidney, thus, there is a risk of accumulation and bleeding in patients with renal impairment. (UFH is excreted mainly via the liver.) Two analyses of trial data confirm that accumulation of LMWH activity is evident in patients with renal impairment, but the data is limited and the effects observed were inconsistent for different products and/or doses, and different creatinine clearance levels.[17,18] Some manufacturers make specific dosing recommendations for use in patients with renal impairment. In such patients, dose reduction and anti-Xa monitoring should be considered.

Dosing in patients with obesity

Treatment regimens of LMWH are based on body weight, which raises concerns when calculating doses for obese patients in whom blood volume is not increased proportionally with weight. Although one study found that in patients weighing up to 165 kg, dosing by weight produced predictable anti-Xa activity,[19] it is wise to monitor anti-Xa activity in obese patients, especially if they have additional risk factors. Caution is also advisable in patients who are underweight.

Fondaparinux (*Arixtra*®)▼ is an anticoagulant, which inhibits factor Xa. It has a long half-life of 17 hours and is given by SC injection once daily. It is currently licensed for the treatment of VTE, and prophylaxis of VTE in medical patients and in patients undergoing major orthopaedic or abdominal surgery.

The British National Formulary and the Summaries of Product Characteristics should be consulted for full prescribing information about specific medicines.

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This bulletin is based on work prepared by
Mari Treharne
Principal Pharmacist Clinical Services
Prince Philip Hospital, Llanelli.